# FORMULATION AND EVALUATION OF SUGAR FREE CHEWABLE TABLETS OF MONTELUKAST SODIUM

***A Dissertation submitted to***

**THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY**

**CHENNAI – 600032**

In partial fulfillment of the requirements for the award of the Degree of

**MASTER OF PHARMACY**

**IN**

**BRANCH - I – PHARMACEUTICS**

***Submitted by***

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***G. Hari Hara Puthra Ayyanar.***

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## ***ABBREVIATIONS***

| | | |
|---|---|---|
| OTC | - | Over The Counter. |
| IR Tablets | - | Immediate Release Tablets. |
| CysLT | - | Cystenyl Leukotrines. |
| OD | - | Once Daily. |
| NSAID | - | Non Steroidal Anti Inflammatory Drug. |
| SSG | - | Sodium Starch Glycolate. |
| CCM | - | Croscarmellose Sodium. |
| CP | - | Crospovidone. |
| % | - | Percentage. |
| mEq | - | Milli Equivalent. |
| Eg | - | Example. |
| Hr | - | Hour. |
| IP | - | Indian Pharmacopoeia. |
| BP | - | British Pharmacopoeia. |
| USP | - | United States Pharmacopoeia. |
| EP | - | European Pharmacopoeia. |
| HCl | - | Hydrochloride. |
| Min | - | Minutes. |
| Sec | - | Seconds. |
| Gm | - | Gram. |
| RH | - | Relative Humidity. |
| $^0C$ | - | Degree Celsius. |
| RPM | - | Rotation Per Minute. |
| Ml | - | Millilitre. |
| µL | - | Micro Litre. |
| Ɵ | - | Theta. |
| SLS | - | Sodium Lauryl Sulphate. |
| ACN | - | Acetonitrile. |
| API | - | Active Pharmaceutical Ingredient. |
| PG starch | - | Pregelatinized Starch. |

| | | |
|---|---|---|
| HPLC | - | High Performance Liquid Chromatography. |
| FT-IR | - | Fourier Transform Infrared Spectroscopy. |
| ICH | - | International Council for Harmonisation. |
| UV | - | Ultra Violet. |
| NCC | - | No Characteristic Change. |
| $Kg/cm^2$ | - | Kilogram Per centimeter square. |
| NMT | - | Not More Than. |
| NLT | - | Not Less Than. |
| SD | - | Standard Deviation. |

## ***CONTENTS***

# CHAPTER -1

# INTRODUCTION

Oral drug has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drug via various pharmaceutical products of different dosage form. The reason that oral route achieved such popularity may be attributed to its ease of administration as well as the traditional belief that by oral administration the drug is well absorbed as the food stuff ingested daily.[1] The oral route of drug administration has been used for both conventional as well as novel drug delivery system. The reasons for this preference are obvious because of the ease of administration and widespread acceptance by patients. The common oral dosage forms include: solid dosage forms like tablets and capsules, etc and liquid dosage forms like mixture, syrup, solution, suspension, emulsion etc. Compared to other oral dosage forms, tablets are manufacturers, choice because of their relatively low cost of manufacture, package and shipment; increased stability and virtual tamper resistance.[2] Among the oral dosage forms, tablets of various types are most used, because it is convenient and safe way of administration. In addition it has advantage in terms of the chemical and physical stability as well as accurate dosing of drug over other dosage forms.[3]

## 1. TABLETS

"It is a solid oral dosage form containing a unit dose of one or more medicaments." Tablet may be defined as solid pharmaceutical dosage form containing drug substance with or without suitable diluents and prepared either by compression (or) molding methods.[4] They are most widely preferred form of medication both by pharmaceutical manufacturer as well as physicians and patients. They offer safe and convenient ways of active pharmaceutical ingredients (API) administration with excellent physiochemical stability in comparison to some other dosage forms and provide accurate dosing. Tablets are usually solid, right circular cylinders, the end surfaces of which are flat or convex and the edges of which may bevelled.[5]

## 1.1 Ideal properties of tablets[6]

The attributes of an acceptable tablet are as follows:

- ✓ The tablets must be sufficiently strong and resistance to shock and abrasion and withstand handling during manufacturing, packing and shipping.
- ✓ Tablet must be uniform in weight and drug content.
- ✓ The drug must be bioavailable. Accurate bioavailability can be obtained from the drug levels after its administration.
- ✓ Tablets must be elegant in appearance and must have characteristic shape, color and other markings necessary to identify the product.
- ✓ Tablets must retain all these function attributes, which include drug stability and efficacy.

### 1.1.1 Advantages of tablets[7]

- ✓ They are easy to administer.
- ✓ They are unit dosage form and they offer the greater capable of all oral dosage forms for the greatest dose precision and the least content variability.
- ✓ Their cost is lowest of all oral dosage forms.
- ✓ Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- ✓ Suitable for large scale production.
- ✓ They lend themselves to certain special release profile products, such as enteric or delayed release products.
- ✓ One of major advantages of tablet over capsule is that the tablet is essentially “tamper proof dosage form”.
- ✓ They have the best combined properties of chemical, mechanical and microbiological stability of all the oral dosage forms.

### 1.1.2 Disadvantages of tablets:

- ✓ Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low density character.
- ✓ Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, poor absorption in the gastrointestinal tract or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet.
- ✓ Difficult to swallow in case of children and unconscious patients.

## 1.2. TYPES OF TABLETS[8]:

Tablets may be uncoated or coated. Uncoated tablets are chewable tablet, effervescent tablet, lozenge tablet, soluble tablet and sublingual tablet. Coated tablets are enteric coated tablet, film coated tablet, implant, sugar coated tablet and modified-release tablet. A broken section of a coated tablet shows a core which is surrounded by a continuous layer of a different texture. The reasons for coating a tablet are:

a) to protect the active ingredients from air, moisture and light.

b) to mask the unpleasant tastes and odor; and

c) to improve the appearance.

**A. Chewable tablet**

The tablet which is intended to be broken and chewed in between the teeth before ingestion. Antacid and vitamin tablets are usually prepared as chewable tablets. It is given to the children who have difficulty in swallowing and to the adults who dislike swallowing.

**B. Effervescent tablet**

The tablet that contains acid substances and carbonate or hydrogen carbonate that react rapidly in the presence of water to release carbon dioxide. Sodium bicarbonate, citric acid and tartaric acid are added to the active ingredients to make the tablet effervescent. This preparation makes the tablet palatable.

**C. Lozenge tablet**

The tablet that is intended to produce continuous effect on the mucous membrane of the throat. There is no disintegrating agent. The quality of the binding agent is increased so as to produce slow dissolution. Suitable sweetening (sugar), coloring and flavoring agents must be included in this formulation. Gum is used to give strength and cohesiveness to the lozenge and facilitating slow release of the active ingredient.

**D. Soluble tablet**

The tablet that dissolves completely in liquid to produce solution of definite concentration. Mouth wash, gargle, skin lotion, douche; antibiotic, certain vitamins and aspirin are given in this formulation.

**E. Sublingual tablet**

The drug which is destroyed or inactivated within the gastrointestinal tract but can be absorbed through the mucosal tissue of the oral cavity is usually given in this formulation. The tablet is required to be placed below the tongue for the slow release of drug. But for immediate effect some medicaments are formulated in such a way to dissolve within 1 to 2 minutes. Nitroglycerin is prepared as sublingual tablet.

**F. Enteric coated tablet**

Some drugs are destroyed by gastric juice or causes irritation to the stomach. These two factors can be overcome by coating the tablet with cellulose acetate phthalate. This polymer is insoluble in gastric contents but readily dissolves in intestinal contents. So there is a delay in the disintegration of dosage form until it reaches the small intestine.

Like coated tablet, enteric coated tablet should be administered in whole form. Broken or crushed form of the enteric coated tablet causes destruction of the drug by gastric juice or produce irritation to the stomach. Enteric coated tablet is comparatively expensive.

**G. Film coated tablet**

The tablet that is covered with a thin layer or film of polymeric substance which protects the drug from atmospheric conditions and mask the objectionable taste and the odor of drug.

**H. Implant tablet**

A small tablet that is prepared for insertion under the skin by giving a small surgical cut into the skin which is stitched after the insertion of the tablet. This tablet must be sterile. The drug used in this preparation is usually water insoluble and the tablet provides a slow and continuous release of drug over prolonged period of time ranging from 3 to 6 months or even more. Contraceptive tablet is formulated as implant.

**I. Sugar coated tablet**

The tablet that contains active ingredient(s) of unpleasant taste may be covered with sugar to make it more palatable. This type of tablet should be administered in whole form; otherwise the patient will experience the unpleasant taste of the active ingredient.

**J. Modified release tablet**

Modified-release tablet is either uncoated or coated. This contains special additives or prepared by special procedure which, separately or together, is intended to modify the rate of release of the drug into the gastrointestinal tract. It prolongs the effect of drug and also reduces the frequency of administration of drug. Several drugs are available in modified release tablet form such as Indomethacin.

## 1.3 PHARMACEUTICAL EXCIPIENTS USED IN THE FORMULATION OF THE TABLETS [9]

Excipients are pharmacologically inactive substances which are added to the tablet formulation for the following purpose.

- ✓ Provide bulk to the formulation.
- ✓ Facilitate drug absorption or solubility and other pharmacokinetic considerations.
- ✓ Aid in handling of "API" during manufacturing.
- ✓ Provide stability and prevent from denaturation.

### 1.3.1 Classification of Excipients for Solid Dosage Form[10]

Additives are usually classified according to some primary function they perform in the pharmaceutical dosage form. Many additives will also often have secondary functions, which may not be of a beneficial nature. The most effective lubricants used are water repellent by their nature, which may retard both disintegration and dissolution. The two major classifications of additives by function include those which affect the compression charteristics of the pharmaceutical dosage form.

A. Fillers and Diluents
B. Binders and Adhesives
C. Disintegrants
D. Glidants
E. Lubricants
F. Antiadherents

And those which affect the bio pharmaceutics, chemical and physical stability and marketing consideration of the pharmaceutical dosage form:

G. Colours
H. Flavours
I. Sweeteners
J. Preservatives
K. Sorbents

**A. Fillers :**

Fillers fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. By increasing the bulk volume, the fillers make it possible for the final product to have the proper volume for patient handling. Good filler must be inert, compatible with the other components of the formulation, non-hygroscopic, soluble, relatively cheap, compactable and preferably tasteless or pleasant tasting. Dibasic calcium phosphate is popular tablet filler.

**Eg:** Lactose, sucrose, glucose, mannitol, sorbitol, calcium carbonate and magnesium stearate.

**B. Binders:**

Binders hold the ingredients in a tablet together. Binders ensure that tablets and granules can be formed with required mechanical strength and give volume to low active dose tablets.

**Eg:** Sugars, cellulose or modified cellulose such as microcrystalline cellulose, hydroxypropyl cellulose, gelatin, polyvinyl pyrolidone, sodium alginate, acacia etc.

**C. Disintegrants:**

Disintegrants expand and dissolve when wet, causing the tablet to break apart in the digestive tract and release the active ingredients for absorption. Disintegrants types include:

- ✓ Water uptake facilitators
- ✓ Tablet rupture promoters

They ensure that when the tablet is in contact with water, it rapidly breaks down into smaller fragments, thereby facilitating dissolution.

**Eg**: Cross linked polyvinylpyrrolidone, sodium starch glycolate, cross linked sodium carboxymethyl cellulose.

**D. Glidants:**

Glidants are used to promote powder flow by reducing interparticle friction and cohesion. These are used in combination with lubricants as they have no ability to reduce die wall friction.

**Eg:** Colloidal silicon dioxide, talc, etc.

**E. Lubricants:**

Lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine. Lubricants also ensure that tablet formation and ejection can occur with low friction between the solid and die wall.

**Eg:** Common minerals like talc or silica and fats, e.g. vegetable stearin, magnesium stearate or stearic acid are the most frequently used lubricants in tablets or hard gelatin capsules.

**F. Antiadherents:**

Antiadherents are used to reduce the adhesion between the powder (granules) and the punch faces and thus prevent sticking to tablet punches.

**Eg:** Talc, starch, silica and magnesium stearate.

**G. Colors:**

Colors are added to improve the appearance of a formulation. Color consistency is important as it allows easy identification of a medication.

**Eg:** Sunset yellow, fast green, brilliant blue, indigo, carmine, erythrosine and eosin.

**H. Flavors:**

Flavors can be used to mask unpleasant taste of active ingredients and to improve the likelihood that the patient will complete a course of medication. Flavors maybe natural (e.g. fruit extract) or artificial. A bitter product may use mint, cherry or anise, a salty product may use peach, apricot or liquorice, a sour product may use raspberry or liquorice and excessively sweet product may use vanilla as flavor.

**I. Preservatives:**

Preservatives are chemical substance used to improve the shelf life of drugs by decreasing or lowering the oxidation of active excipients and by reducing microbial production. Some typical preservatives used in pharmaceutical formulations are;

**Eg:** Methyl, propyl, benzyl, butyl p- hydroxy benzoate.

**J. Sweeteners:**

Sweeteners are added to make the ingredients more palatable, especially in chewable tablets such as antacid tablet or liquids like cough syrup. Sugar can be used to disguise unpleasant tastes or smells.

**Eg**: Aspartame, sucralose, glycerin, mannitol, sorbitol, acesulfame potasium, saccharin sodium etc.

## 1.4 STEPS INVOLVED IN TABLET FORMULATION[11]

- ✓ **Dispensing**: Each ingredient in the tablet formula is weighed and accurately dispensed as per dose. This is one of the critical steps in any type of formulation process and should be done under technical supervision.
- ✓ **Sizing:** Formulation ingredients must be in finely divided form, otherwise, size reduction should be carried out for better flow property and easy mixing.
- ✓ **Powder blending:** Powders are mixed using a suitable blender to obtain a uniform and homogeneous powder mix. The drug substance and excipients are mixed in geometric dilution.
- ✓ **Granulation**: Here small powder particles are gathered together into layers and permanent aggregates to render them into free flowing states.
- ✓ **Drying and dry screening**: Screened wet granules need to be dried for a particular time period in tray drier or fluid bed drier at controlled temperature not exceeding 55°C. Dried granules are screened through the appropriate mesh screen.
- ✓ **Tablet compression:** This step involves the compression of granules into a flat or convex, round, oblong or unique shaped, scored or unscored tablet; engraved with an identifying symbol and/ or code number.
- ✓ **Coating:** Tablets and granules are coated if there is need to mask the unpleasant taste/odour of some drug substance or to increase the aesthetic appeal of uncoated tablets as well as to modify the release or control the release of drug substance from tablets. This is achieved by enclosing or covering the core tablet or granules with coating solutions.

## 1.5 TECHNIQUES METHODS USED IN TABLET FORMULATION:

Tablets are commonly manufactured by

- ✓ Wet granulation method
- ✓ Dry granulation method
- ✓ Direct compression method.

One important requirement during tableting is that the drug mixture should flow freely from the hopper of the tableting machine into the dies to enable high speed compression the powder mix into tablets.

### 1.5.1 Manufacture of tablets by wet granulation method

Wet granulation is a widely used method for the production of compressed tablets. It is essentially a process of size enlargement involving several steps and the use of an adhesive substance known as binder. The granules produced using this method has a greater probability of meeting all the physical requirements for tablet formation.

### 1.5.2 Manufacture of tablets by dry granulation method

The formation of granules by compacting powder mixtures into large pieces or compacts which are subsequently broken down or sized into granules (often referred to as dry granulation, double compression or pre-compression) is a possible granulation method which, however, is not widely used in the manufacture of tablets. This method is used when tablet excipients have sufficient inherent binding properties. The procedure can also be used as a means to avoid exposure of drug substances to elevated temperatures (during drying) or moisture.

### 1.5.3 Manufacture of tablets by direct compression method

As its name implies, direct compression involves direct compression of powdered materials into tablets without modifying the physical nature of the materials itself. The technology involved in this method assumes great importance in the tablet formulations, because it is often the cheapest means in the production of tablets.

Direct compression method avoids many of the problems associated with wet and dry granulations. Its successful application in tablet formulation rests on two fundamental issues:

- ✓ The availability of suitable excipients.
- ✓ The availability of suitable machinery.

### 1.5.4 Tablet compression[12]:

After the preparation of granules (in case of wet granulation) or sized slugs (in case of dry granulation) or mixing of ingredients (in case of direct compression), they are compressed to get final product. The compression is done either by single punch machine (stamping press) or by multi station machine (rotary press). The different stages of compression process include filling, metering, compression.

## 1.6 EVALUATION OF TABLETS[13]:

The tablet is the most popular dosage form as they were easy in preparation compared to any other type of dosage forms. But the major drawback exists in its manufacturing. If any minor problem occurs during their manufacturing, then the whole batch of the unit should be discarded. It is necessary to avoid any sort of errors during its manufacturing and as a result evaluation of tablets is very important before dispatching of a batch. Evaluation of tablets can be carried out by official and unofficial tests.

**a) Unofficial tests**

- ✓ Appearance
- ✓ Size and Shape
- ✓ Organoleptic properties
- ✓ Uniformity of thickness
- ✓ Hardness
- ✓ Friability

**b) Official tests**

- ✓ Weight variation test
- ✓ Content uniformity
- ✓ Disintegration test
- ✓ Dissolution test

# 1.7 CHEWABLE TABLETS

Chewable tablets are an immediate release (IR) oral dosage form intended to be chewed and then swallowed by the patient rather than swallowed whole. They should be designed to have a pleasant taste and be easily chewed and swallowed.[14] Chewable tablets should be safe and easy to use in a diverse patient population, pediatric, adult or elderly patient, who is unable or unwilling to swallow intact tablets due to the size of the tablet or difficulty with swallowing. The availability of safe, easy-to-use dosage forms is important in clinical practice. Chewable tablets are available for many over-the-counter (OTC) and prescription drug products.[15] The United States Pharmacopeia (USP) recognizes and differentiates between two types of chewable tablets: (1) those that may be chewed for ease of administration and (2) those that must be chewed or crushed before swallowing to avoid choking and/or to ensure the release of the active ingredient. The concepts in this guidance are applicable to both types of chewable tablets.[16]

**Advantages of Chewable Tablets:[17]**

- ✓ Patient convenience.
- ✓ Substitute for liquid dosage forms.
- ✓ Improved patient acceptance.
- ✓ Better bioavailability.
- ✓ Provides proper unit dosage form of medication.

**Disadvantages of Chewable Tablets:**

- ✓ Bad tasting drugs should not be suitable.
- ✓ Drugs having high dosage levels should be difficult to formulate.
- ✓ These tablets may contain sorbitol which can cause diarrhoea and flatulence.
- ✓ Prolonged chewing of these tablets results in pain in facial muscles.
- ✓ They require proper packaging for safety and stability of drug.

The several aspects to be considered in formulation of chewable tablets are shown in fig.1

**Flow chart of Various Aspects to be Considered in Connection with Chewable Tablets**

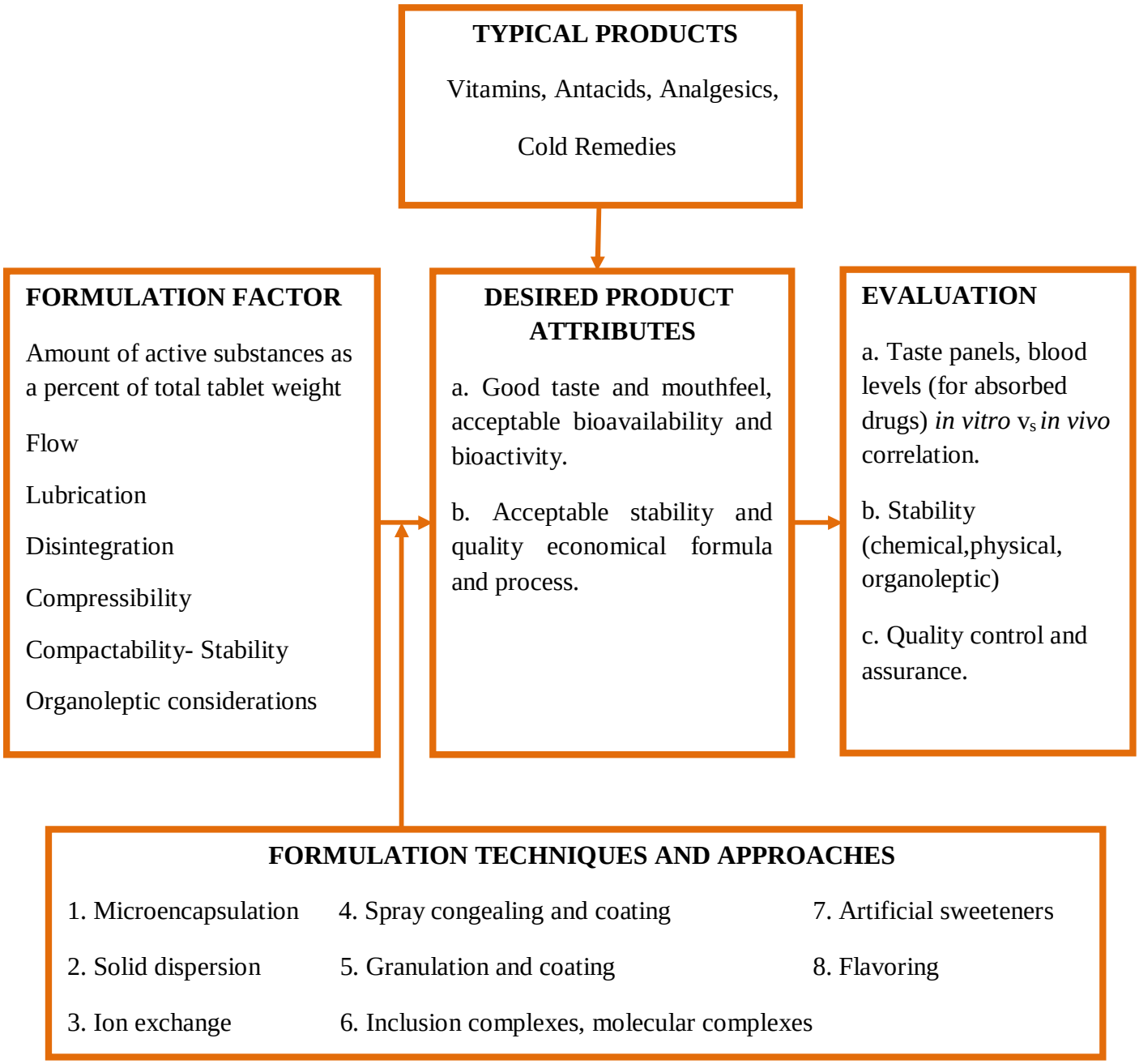


**Fig 1: Various Aspects to be Considered in Formulation of Chewable Tablets**

## 1.7.1 GENERAL FORMULATION FACTORS TO BE CONSIDERED IN THE FORMULATION OF CHEWABLE TABLETS [18]

Various factors are involved in the formulation of chewable tablets. The major formulation factors are flow property, lubrication, disintegration, organoleptic properties, compressibility, compatibility and stability, which are common to regular (swallowed) and chewable tablets; however, organoleptic properties of the active drug substances are primary concern here. A formulator may use one or more approaches to arrive at a combination of formula and process that results in product with good organoleptic properties. Such a substance must have acceptable flow, compressibility and stability characteristics.

### A. Taste and Flavor

Physiologically, taste is a sensory response resulting from a chemical stimulation of the taste buds on the tongue. There are four basic type of taste; salty, sour, sweet and bitter. Salty or sour tastes are derived from substances capable of ionizing in the solution. Many organic medicinal compounds stimulate a bitter response even though they may not be capable of ionizing in an aqueous medium. Most saccharides, disaccharides, some aldehydes and few alcohols give a sweet taste. Substance incapable of producing a sensory stimulation of the buds is known as tasteless. The term flavor generally refers to a specific combined sensation of taste and smell. For example, sugar has a sweet taste, but no flavor, whereas honey has a sweet taste and a characteristic smell.

### B. Aroma[19]

Pleasant smells are generally referred to as aromas. For example, a well formulated, orange-flavored chewable tablet should have a characteristic sweet and sour taste and aroma of fresh orange.

### C. Mouth-Feel

This term is related to the type of sensation or touch that a tablet produce in the mouth upon chewing. As such, it has nothing to do with chemical stimulation of olfactory nerves or taste buds. However, for a formulation to be successful, the overall effect in the mouth is important. In general, gritty (e.g., calcium carbonates) or gummy texture is undesirable, whereas soothing and cooling sensation (e.g., mannitol) with smooth texture is preferred.

**D. After Effects** [20]

The most common after effect of many compounds is after taste. For example, some irons leave a "rusty" after taste; saccharin in high amounts tends to leave a bitter after taste. Another common after effect is a numbing sensation of a portion or the whole surface of the tongue and mouth. Bitter anti-histamines like Pyribenzamine hydrochloride and Promethazine hydrochloride are typical of this class drugs.

## 1.7.2 ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES OF ACTIVE DRUG IN THE FORMULATION OF CHEWABLE TABLETS[21]

Wherever feasible and practical, the first step in the formulation of chewable tablet is to obtain a complete profile of the active drug. This usually leads to the most efficient formulation of a stable and quality product as the drug usually dictates the choice of fillers, carriers, sweeteners, flavor compounds and other product modifiers. The drug profile ideally should contain information on the following:

**A. Physical Properties**

- ✓ Color
- ✓ Odor
- ✓ Taste, after-taste and mouth-feel
- ✓ Physical form: Crystal, powder, amorphous solid, oily liquid, etc.
- ✓ Melting temperature
- ✓ Polymorphism
- ✓ Moisture content, aqueous solubility
- ✓ Active drug stability

**B. Chemical Properties**

- ✓ Chemical structure and chemical class
- ✓ Major reactions
- ✓ Major incompatible compounds
- ✓ Drug dose

## 1.7.3 "TASTE"- A NECESSARY REQUIREMENT FOR CHEWABLE TABLETS [22]

### A. Physiology of Taste

Generally human tongue contains 50-100 numbers of taste buds. It has onion shaped structure. Chemical from foods or orally ingested medicaments are dissolved by saliva via taste pores. They either interact with surface proteins known as taste receptors or ion-channels. Taste sensation can be expressed as a feeling by an individual when something is given into mouth in order to ascertain the whole component. There are generally four fundamental types of taste.

- ✓ Sweet and salty, mainly at the tip of tongue
- ✓ Sour, at the side of tongue
- ✓ Bitter, at the back of the tongue

### B. Taste Masking

Taste masking is defined as a reduction of undesirable taste that would otherwise exist. Taste masking can be achieved using taste masking agents, specific flavors and sweeteners. Sweeteners are essential to complete the experience and produce a pleasant taste of the product. This is one of the major limiting factors in the formulation of oral dosage forms having unpleasant taste. Flavor masking and processing approaches are two primary methods to overcome this problem. Flavor masking generally include addition of flavor, sweetener, lipid and acids.

### C. Techniques for Taste Masking

Taste-masking techniques often go hand in hand with the formulation technology. In short, they need to be mutually compatible. For example, coated particles obtained after fluid-bed coating should be able to withstand the tablet compression process used for the final dosage form (tablet) manufacturing. The commonly used industrial techniques/methods of taste-masking include,

- ✓ Organoleptic methods
- ✓ Polymer coating
- ✓ Hot-melt extrusion
- ✓ Microencapsulation
- ✓ Complexation
- ✓ Spray-drying

## 1.7.4 GENERAL EXCIPIENTS USED IN THE FORMULATION OF CHEWABLE TABLETS[23]

The acceptability in the formulation of chewable tablets will be primarily determined by taste and to a lesser degree, appearance. Therefore, appropriate selection and use of components that impact on these properties are of extreme importance. Major excipients, such as fillers or direct compaction vehicle have the major role in the outcome of these concerns. Many of the sweeteners commonly used in the tablet formulation are especially applicable for use in chewable tablets due to their ability to provide the necessary properties of sweetness and chewability. In general all these excipients fall under the sugar category, although a combination of bland excipients with artificial sweeteners may provide a satisfactory alternative. Some common chewable tablet sweeteners are brown sugar, compressible sugar, honey, dextrose, lactose, mannitol, sorbitol, etc.

**A. Sweeteners**

- ✓ **Dextrose**

Dextrose is the sugar obtained through the complete hydrolysis of starch. Its sweetness level is approximately 70% that of sucrose and is available in both anhydrous (but hygroscopic in nature) and monohydrated form.

- ✓ **Lactose**

Lactose is the monosaccharide produced from whey, a byproduct of the processing of cheese. Although generally acknowledged as the most widely used pharmaceutical excipient in the world, its applicability to chewable tablets is less, due to its extremely low sweetness level. This deficiency requires the addition of an artificial sweetener of sufficient potency to overcome lactose's blandness.

- ✓ **Mannitol**

Mannitol is a white, crystalline polyol approximately 50% as sweet as sucrose. It is freely soluble in water and, when chewed or dissolved in the mouth, imparts a mild cooling sensation due to its negative heat of solution.

**B. Flavors**

Taste is almost certainly the most important parameter in the evaluation of chewable tablets. Taste is a combination of the perceptions of mouth feel, sweetness and flavor. Flavoring agents are available in a variety of physical forms from a large number of suppliers specializing in these materials. Virtually all offer technical support services, which will be addressed in the section on flavor formulation.

Various groups of flavors for general baseline taste types are presented in table 1.

**Table: 1 Flavor Groups for General Baseline Taste Types**

| | |
|---|---|
| **Sweet** | Grape, berries, honey, vanilla |
| **Sour (acidic)** | Citrus, liquorice, strawberry, cherry |
| **Salty** | Buttery, spice, mixed citrus, mixed fruit |
| **Bitter** | Liquorice, wine, mint, nut, fennel, grapefruit |

**C. Colorants**

- ✓ To increase aesthetic appeal
- ✓ To mask non uniform colour of raw materials
- ✓ Aid in product identification and differentiation

## 1.7.5 GENERAL METHODS OF MANUFACTURING CHEWABLE TABLETS[24]

The chewable tablets were prepared by using the following methods:

1. Non aqueous Granulation/Dry Granulation
2. Aqueous Granulation/Wet Granulation
3. Direct Compression

**Granulation**

Granulation is the process in which primary powder particles are made to adhere to form larger, multi-particles entities called granules. Pharmaceutically granules have size range between 0.2 to 4.0 mm. Granulation is used to improve flow and compressibility of powders and to prevent segregation of the blend components. Granulation is mainly done by using two techniques.

**Dry Granulation**

It is the novel method for semi-automatic production of granules. The method is applicable to any solid dosage pharmaceutical products. Dry granulation method replaces existing solid dosage form development and manufacturing technologies offering more rapid development and better quality. In this process, the powder mixture is compressed without the use of heat and solvent. Two methods are used for dry granulation. The more widely used is slugging where the powder is recompressed and the resulting tablets are milled to yield the granules.

**Wet Granulation**

Wet granulation is the most commonly used granulation method. This process involves wet massing of powder blend with a granulating liquid, wet sizing and drying. The granulating liquid contains a solvent which must be volatile so that it can be removed by drying and must be non-toxic in nature. Typical liquid include water, ethanol and Isopropyl alcohol. In the traditional wet granulation method the wet mass is forced through a sieve to produce wet granules which are subsequently dried.

**Direct Compression**[25]

Direct compression is the most popular choice because it provides the shortest, most effective and least complex way to produce tablets. This method is mainly used when a group of ingredients can be blended. This is more suitable for moisture and heat sensitive API.

## 1.7.6 EVALUATION PARAMETERS FOR CHEWABLE TABLETS[26]

**A. Physical Evaluation**

It involves the following:

1. Tablet physical appearance
2. Hardness
3. Friability
4. Disintegration
5. Dissolution

**B. Chemical Evaluation**

It involves the following:

1. Assay of drug content
2. Dosage uniformity
3. *In vitro* and *In vivo* evaluation

## 1.7.7 STABILITY TEST FOR CHEWABLE TABLETS[27]

Stability testing of dosage forms or drug products is carried out to evaluate time dependent changes. Accelerated stability testing is used to predict quickly the potential changes that may occur in a product. There are three areas of major concern in the stability testing of chewable tablets such as organoleptic, chemical, physical parameter evaluation. The data obtained from chemical evaluation of the tablets at elevated temperature and humidity, stress conditions are most useful.

**Other tests in the stability program would include:**

- ✓ Active drug content determination.
- ✓ Changes in physical characterization of the tablets.
- ✓ Changes in the tablet hardness, friability, dissolution rate and extent of dissolution.
- ✓ Moisture content of the tablets.
- ✓ Stability of the coating systems.
- ✓ Stability of the colorants.

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# CHAPTER-2

# REVIEW OF LITERATURE

**Shruthi.K *et al.*, (2013)**[28] formulated and evaluated Montelukast sodium chewable tablets prepared by wet granulation method using different concentrations of xanthan gum, karaya gum, modified karaya gum as diluents and sodium starch glycolate (SSG) as disintegrant. The tablets were evaluated for various parameters such as general appearance, diameter, thickness, hardness, weight variation, wetting time, friability, disintegration time, drug content estimation and *in vitro* dissolution studies. The results were found to be satisfactory and within specifications. Formulation F12 containing modified karaya gum 30% and SSG 4% was selected as optimized formulation, as it showed complete drug release in 90 minutes. Comparison studies were performed for optimized and marketed formulations and difference (F12) and similarity factors (f2) values were found to be 3.82 and 75.12% respectively. The optimized formulation (F12) was subjected to stability studies for three months as per ICH guidelines and showed good physical stability with significant changes in physical appearance and quality control tests. Hence it can be concluded formulation F12 containing modified karaya gum 30% and SSG 4% fulfilled all the criteria for chewable tablets.

**Errolla Mahesh *et al.*, (2009)**[29] formulated Montelukast sodium chewable tablets by using novel co-processed superdisintegrants consisting of crospovidone and sodium starch glycolate in the different ratios (1:1, 1:2 & 1:3) and vice versa. Montelukast sodium is a drug of choice in treatment of asthma and allergic rhinitis. Drug compatibility with excipients was checked by FT-IR studies. The flow properties of the powder blends were found to be within prescribed limits and indicated good flow property. All the formulations were subjected to post compression parameters. Hardness and friability test indicated that tablets had a good mechanical strength and resistance. Drug content was found to be in the range of 93.51 to 98.79 %. The wetting time of all formulations were found to be in the range of 20 to 55 sec. Among all the designed formulations, formulation F9 was found to be promising and showed an *in vitro* disintegration time of 25 sec, which facilitates faster disintegration in the mouth. When compared to marketed product, the formulation F9 containing co-processed superdisintegrants (1:3 mixture of sodium starch glycolate and crospovidone) emerged as the overall best formulation based on drug release characteristics. Short-term stability studies on

promising formulation F9 indicated that there were no significant changes in hardness, drug content and *in vitro* drug release.

**Kanakadurga Devi. N *et al.*, (2012)[30]** formulated and evaluated fast mouth dissolving chewable tablets of Montelukast sodium by direct compression method with three superdisintegrants (i.e) polyplasdone XL10, Ac-Di-Sol and Primojel. The pure drug and formulation blend was examined for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The tablets were evaluated for hardness, tensile strength, drug content, friability and were found satisfactory. Disintegration time in the oral cavity was also tested and was found to be around 9 sec. Based on dissolution rate the disintegrants can be rated as polyplasdone XL10 > Ac-Di-Sol > Primojel. Hence polyplasdone XL10 was recommended as suitable disintegrant for the preparation of direct compression melt-in-mouth tablets of Montelukast sodium. All the dissolution parameters were calculated and compared with market tablet. An increase in the dissolution rate was observed with M8 formulation when compared to market tablet. Hence it was concluded that the rapidly disintegrating tablets of Montelukast sodium with proper hardness, rapid disintegration in the oral cavity with enhanced dissolution rate can be made using polyplasdone XL10.

**Alaa Eldin A. Kassem *et al.*, (2017)[31]** prepared fast dissolving sublingual films of Montelukast sodium (MS) using solvent casting technique. Tween 80 was used as solubilizing agent, Propylene glycol as plasticizer and mannitol as sweetener. The compatibility between the drug and film formers was investigated using Fourier Transform Infrared spectroscopy and Differential Scanning Colorimetry studies. The developed formulations were characterized for physico-mechanical properties and pharmacokinetic parameters. Simple, validated HPLC analysis method was used to compare the bioavailability of the chosen prepared sublingual film containing 5% w/w hydroxyl propyl methylcellulose E15 and the commercial product (Kokast®) after their sublingual administration to albino rabbits. The results showed that all physico-mechcanical properties and pharmacokinetic parameters were within the acceptable limits. Hence it can be concluded that formulation F5 (5 %w/w HPMC) is very much promising as sublingual film of MS with excellent physical appearance, suitable weight and thickness values, least disintegration time, highest dissolution rate, highest *C*max and AUC and best relative bioavailability.

**Jahufar Sathik *et al.*, (2011)[32]** developed and evaluated bilayer tablet of Montelukast sodium and Levocitrazine HCl using superdisintegrants such as croscarmellose sodium and starch granules. IR spectrum revealed that there is no disturbance in the principle peaks of pure drugs of Montelukast sodium and Levocetrizine HCl. The angle of repose was ranged from 25.0˚±1.40 to 31.4˚±0.97 for Montelukast sodium and 25.2˚±1.40 to 29.5˚± 0.68 for Levocetrizine HCl. The compressibility index was found in the range of 11.6 to 22.2 for Montelukast sodium and 14.1 to 27.8 for Levocetrizine HCl. Hausner's ratio was found to be 1.143 to 1.287 for Montelukast sodium and 1.41 to 1.46 for Levocetrizine HCl. The results of the angle of repose indicates good flow property of the granules and the values of compressibility index further showed support for the flow property. The prepared tablets were evaluated for hardness, friability, weight variation, drug content uniformity and *in vitro* release studies. The results were found to be within the limits. The stability studies were carried out for the optimized formulation for three months and it show acceptable results. Among the various formulations prepared, Formulation F8 with croscarmellose sodium (20%) shows minimum disintegration time and improved dissolution properties and emerged as best formulation. This is because of the dual action of wicking and swelling property of disintegrants. Hence, it is finally concluded that, the bilayer immediate release tablets of Montelukast sodium and Levocetrizine HCl can be used for alternative dosage form in the effective treatment of patients suffering from allergic rhinitis and bronchial asthma.

**Hosseinali Tabandeh *et al.*, (2013)[33]** developed Ferrous fumarate chewable tablets by simplex experimental method. The mathematical experimental design was used as the formulation approach. Different series of formulations based on single filler (Lactose granule, mannitol granule and three Avicels) were prepared and evaluated. The total filler percentage in formulation was kept constant at 40% and simplex lattice mixture design was used with percentages of each of the three selected fillers as factors and hardness, friability and taste of the resulted tablets as responses. The statistical analysis and optimization were performed by Design Expert software using responses in suggested experimental runs. Two-way analysis of variance and Scheffe Post-Hoc test showed that both the type and amount of fillers were effective on hardness. Avicel PH 301 was selected as the filler for imparting higher hardness and lactose and mannitol granules for imparting good taste and mouth feel to tablets. The mathematical optimization suggested the acceptable formulations of Ferrous fumarate chewable tablets. The mathematical experimental design is suggested as a promising efficient method for optimization of pharmaceutical formulation projects with multiple goals.

**M. Rajesh *et al.*, (2012)[34]** developed Albendazole chewable tablets by wet granulation method using two superdisintegrants such as croscarmellose sodium and sodium starch glycolate. A total of eight formulations were prepared and the granules were evaluated for precompression parameters such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The formulated tablets were evaluated for diameter, thickness, hardness, weight variation, friability, disintegration, drug content and drug release study. The results showed that all the physical parameters were within the acceptable limits. IR spectral studies revealed that there was no interaction between the drug and excipients. The *in vitro* release study of formulation F8 showed 81.03% drug release at the end of 30 min. The stability studies for the formulation F8 showed no significant change in disintegration time, drug content and percentage drug release after stored at $40^{o}\pm2^{o}C/75\pm5\%RH$ for a period of 30 days. Hence it can be concluded that formulation F8 showed better characteristics of chewable tablets.

**V. Anil kumar *et al.*, (2016)[35]** formulated and evaluated chewable tablets of Almotriptan by direct compression method by using various superdisintegrants like (Crospovidone, croscarmellose sodium, sodium starch glycolate). All the tablets were subjected to weight variation, drug content uniformity, lock length, dissolution, drug excipients interaction and short-term stability studies. There was no difference in the position of the absorption bands, hence providing evidence for the absence of any chemical incompatibility between pure drug with the excipients. The bulk density and tapped density for all formulation (F1 –F9) varied from 0.423 - 0.485 $gm/cm^3$ and 0.501 - 0.593 $gm/cm^3$ respectively. The results of carr's consolidate index or % compressibility index and hausner's ratio for the entire formulation (F1 – F9) blend range from 15.5- 19.1% and 1.10-1.28 respectively, shows fair flow properties. All the tablets showed similar color, odour, taste and physical appearance. The hardness values ranged from 3.0-3.5 $kg/cm^2$ for formulations (F1-F9). The entire tablets passed the weight variation test, as the average % weight variation was within the Pharmacopeial limit (±7.5%). The concentration of the drug in all the formulations with different polymers was found to be 97.35 – 99.58%. It was within the IP limit. It can be concluded that formulated immediate release tablets of Almotriptan exhibited good physical parameters. The overall results indicated that formulation F6 with croscarmellose (7.5%) had a higher edge with good palatability compared to other formulations.

**Fatima, *et al.*, (2016)[36]** developed and evaluated chewable tablets of Clarithromycin using ion exchange resins. The present investigation aims at taste masking of the bitter Clarithromycin using ion exchange resins, which forms complexes, inhibiting its release in saliva. The drug-resin complex loading process was optimized for the content of resin, activation, swelling time, stirring time, influence of pH and temperature for maximum drug loading and was subjected to differential scanning colorimetry to confirm the complex formation. These complexes were used to prepare chewable tablets and to evaluate the taste. Acid-activated resins comprising of Indion 204, Indion 234 and Tulsion 335 with drug: resin ratio of 1:2, stirred in solution of pH 7-8 at 70°C for 6 h had a maximum drug loading and masked the bitter taste of Clarithromycin. The drug-resin complex was formulated into chewable tablet formulations (F1-F9) and evaluated. Various pre and post-compression parameters were found to be within permissible limits. Formulations F3, F6 and F9 containing 1:2 ratios of drug-resin complex of Indion 204, Indion 234 and Tulsion 335 revealed maximum taste masking. This was further confirmed by treatment of taste evaluation scores of the volunteers by ANOVA, Dunnets multiple comparison test and Tukey's multiple comparison test. All the three optimized formulations had a significant difference of $P<0.001$ when compared to control F10. Formulation F6 was emerged as a best formulation. Hence it was concluded that Ion exchange complexation could efficiently mask the bitter taste of Clarithromycin and achieve palatable taste suitable for pediatric use.

**Sumalatha *et al.*, (2015)[37]** formulated and evaluated polyherbal chewable tablets for reducing nicotine dependence. Plants have always been an experimental source of drugs and many of the currently available drugs have been derived directly or indirectly from them. Following all data and knowledge, chewable tablets for smoking cessation was prepared using Ginger (Zingiber officinale), Tulsi (Ocimum sanctum), Almond (Prunus amygdalis), Fennel (Foeniculum vulgare), Cinnamon (Cinnamomum zeylanicum), Clove (Eugenia caryophyllus), Cardamom (Elettaria cardamomum) with acacia gum 5% w/v) as a binding agent, sorbitol as sweetening agent. Poly herbal chewable tablets were prepared by wet granulation technique by using acacia gum 5% w/v) as a binding agent. Tablets were evaluated for weight variation test, friability, hardness; time required for complete chewing and all the values are found within acceptable limits. It can be concluded that the selected formulation of poly herbal chewable tablets has acceptable physicochemical features and may be considered as herbal medication for reducing nicotine dependence.

**Mahalaxmi Rathnanand *et al.*, (2013)[38]** formulated and evaluated Metformin chewable tablets using stevia by three methods *viz* non aqueous granulation, aqueous granulation and direct compression. Various evaluation parameters like thickness, hardness, friability, weight variation and drug content of the formulations were tested and found to be satisfactory. All the formulations showed similar thickness. Tablets from different formulations showed hardness in the range of 4 - 4.3 $Kg/cm^2$. All formulations passed the USP requirement in terms of weight variation and drug uniformity. All the formulations showed disintegration time below 15 min. Release profile of the optimized formulation prepared by wet granulation technique showed satisfactory release within 30 min. The variation in the dissolution rate of Metformin chewable tablets made by different techniques were in the following order, direct compression< non-aqueous granulation< aqueous granulation. Hence it can be concluded that chewable tablets of Metformin HCl prepared by wet granulation method had faster dissolution rate within 30 min compared to remaining batches.

**Bharat *et al.*, (2012)[39]** prepared Albendazole chewable tablets by three methods *viz.* non aqueous granulation, aqueous granulation and direct compression. Tablets prepared by these three methods were evaluated for different parameters such as Average weight, hardness, carr's index, tapped density, friability, disintegration, water content, *in vitro* dissolution *etc.* All the parameters were found within the specifications. All the tablets showed good hardness. Batch 'AG' had minimum hardness ($5.1\pm0.10$ $kg/cm^2$) while 'DC' had maximum hardness ($5.5\pm0.09$ $kg/cm^2$). The friability was less than 0.2% for all the formulations and was satisfactory. Assay value of all prepared batches of Albendazole tablets were within the range of 90% to 110% of stated amount of Albendazole. From the data obtained it was found that 88.8% of drug was released for the trial 'DC' at 30 min while other trials 'NG' and 'AG' had shown 81% & 80.5% drug release at 30 min respectively. The variation in the dissolution rate of Albendazole tablets was in the following order AG<NG<DC. The study revealed that the tablets prepared by 'Direct compression' had faster dissolution rate while compared to remaining batches and marketed product.

**Swati Jagdale *et al.*, (2010)[40]** formulated and evaluated chewable tablets of Levamisole which is used in the treatment of worm infestations. The chewable tablets of Levamisole were prepared by using lactose or mannitol along with sodium starch glycolate as superdisintegrant especially for paediatric use. Sodium saccharin and vanilla were used as

sweetening agent and flavouring agent respectively. It was observed that the formulation containing lactose shows less disintegration time than formulation containing mannitol. The overall results revealed that Levamisole chewables tablet containing lactose and sodium starch glycolate showed minimum disintegration time, sufficient hardness, pleasant taste, better dissolution rate and was considered as best formulation.

**Kathiresan K *et.al.*, (2010)[41]** formulated and evaluated 5 batches of Loratadine chewable tablets. Loratadine, which is histamine H1 receptor antagonist was used in the treatment of allergic rhinitis and urticaria. Results showed that thickness, weight variation, friability, hardness and content uniformity of all formulations were within the acceptance limits. But in the *in vitro* dissolution study, formulations 1, 2 and 5 demonstrated better cumulative drug release than formulations 3 and 4. However, cumulative drug release of formulation 5 was comparable with innovator than formulations 1 and 2. Hence the study concludes that Loratadine chewable tablets formulated using Avicel CE 15 and starch paste showed better characteristics of chewable tablets.

**M. Rajesh *et al.*, (2018)[42]** formulated and evaluated sugar free Sucralfate chewable tablets by wet granulation method using croscarmellose sodium and sodium starch glycolate as superdisintegrants and neotame as non calorific sweetener. The formulated tablets were evaluated for thickness, hardness, weight variation, friability, disintegration test, drug content, acid neutralizing capacity and *in vitro* dissolution studies. The FT-IR spectral studies revealed that there was no interaction between the drug and excipients. Formulation SCT-7 showed rapid drug release (92.3%) at the end of 25 minutes and good acid neutralizing capacity (17.44 mEq) compared to other formulations. Hence it can be concluded that formulation SCT-7 containing combination of two superdisintegrants (croscarmellose sodium and sodium starch glycolate) was found to be the better one which satisfied all the criteria for chewable tablets.

**Sabina Akhtar *et al.*, (2017)[43]** developed chewable multivitamin tablets by direct compression method and to ensure that they are easily crushed by chewing. The excipients used in this study are mannitol, sucrose, starch, talc, magnesium stearate and vanilla powder. Multivitamins used are ascorbic acid, riboflavin, nicotinamide, thiamine HCl. The powder blend was evaluated for various precompression parameters. The formulated tablets were

evaluated for post compression parameters. The tablets showed immediate drug release and all the parameters were found within the specification. Drug content of ascorbic acid was found to be (103.62% - 108.84%), riboflavin (99.88% - 112.02%), nicotinamide (93.44% - 100.31%) and thiamine HCl (105.94% - 108.5%). The results conclude that the multivitamin chewable tablets could be successfully prepared by direct compression method.

**A Halder *et al.*, (2013)[44]** formulated and evaluated chewable tablets of Loperamide by wet granulation technique using microcrystalline cellulose and crosscarmellose sodium. The prepared tablets showed good physical characteristics, drug content and percentage of drug release. Among the 6 formulations, F1 showed better drug release (96%) and drug content (98.38%). Further, F1 was selected for the method development and validation purpose. The validation data indicates the suitability of the developed chromatographic method which is easier and cost effective than the other reported and official methods.

**Sree Giri Prasad *et al.*, (2012)[45]** formulated Montelukast chewable tablets by both wet granulation and direct compression methods using suitable excipients. A total of eight formulations were prepared and the granules were evaluated for precompression parameters. The formulated tablets were evaluated for post compression parameters. The results showed that all the physical parameters were within the acceptable limits. I.R spectral studies revealed that there was no interaction between the drug and excipients. The *in vitro* release study of formulation F7 showed 98.85% drug release at the end of 30 min. The stability studies for the formulation F7 stored at $40^0$ C / 75% RH and room temperature for three months showed no significant changes. Hence it can be concluded that formulation F7 prepared by direct compression method showed better characteristics of chewable tablet.

**Dhruba Sankar *et al.*, (2014)[46]** developed and evaluated Paracetamol and Metoclopramide hydrochloride chewable tablets by wet granulation method to study the effect of different proportion of Aerosil, croscarmellose sodium, crospovidone and neem gum. Maize starch was used as binding agent. Tartrazine was used as coloring agent. Aspartame and vanilla flavor were used as sweetening agent and flavoring agent respectively. Several physicochemical parameters like thickness, diameter, hardness, % weight variation, % loss in weight, drug content, disintegration time, *in vitro* dissolution studies, kinetics of drug release and stability study for all the formulations were studied and were found within the acceptance limits. Formulation F10 containing neem gum (1%) showed best cumulative drug release for

Paracetamol (99.55%) and Metoclopramide hydrochloride (98.59%) and emerged as best formulation.

**D Kumar *et al.*, (2014)[47]** developed and evaluated Paracetamol and Metoclopramide hydrochloride chewable tablets by wet granulation method to study the effect of different proportion of Aerosil, croscarmellose sodium, crospovidone and moringa gum. Maize starch was used as binding agent. Several physicochemical parameters like thickness, diameter, hardness, % weight variation, % loss in weight, drug content, disintegration time, *in vitro* dissolution studies, kinetics of drug release and stability studies for all the formulations were studied and were found within the acceptance limits. Formulation F7 containing moringa gum (1%) showed the best cumulative drug release for Paracetamol (97.32%) and Metoclopramide hydrochloride (96.45%) and emerged as best formulation.

**Ashok Kumar *et al.*, (2014)[48]** formulated Pentoxifylline loaded chewable tablets for the treatment of peripheral vascular disease. The chewable tablets were prepared by using wet granulation technique. Lactose and mannitol were used as diluents with different concentration of sodium starch glycolate (SSG) as superdisintegrant. Prepared granules were subjected to precompression studies like angle of repose and compressibility index. The compressed formulations were then evaluated for appearance, thickness, weight variation, hardness, friability, drug content uniformity, wetting time, disintegration time and *in vitro* drug release profile. The *in vitro* drug release profile was carried out in phosphate buffer (PBS pH 6.8) at 37±0.1ºC using USP paddle Type II. The results of all evaluation parameters were found within acceptable limits. The formulation containing 4.0% w/w of sodium starch glycolate showed minimum disintegration time and showed 97.82 % drug release in 30 minutes than other formulations and emerged as the overall best formulation.

**Jayapal Reddy *et al.*, (2011)[49]** formulated and evaluated polyherbal chewable tablets for cough remedy. Plants have always been an exemplary source of drugs and many of the currently available drugs have been derived directly or indirectly from them. Chewable tablets for cough remedy was prepared using Liquorice (Glycyrrhiza glabra), Ginger (Zingiber officinale), Black pepper, Tulsi (Ocimum sanctum), Pudina (Mentha piperita), Fennel (Foeniculum vulgare), Cinnamon (Cinnamomum zeylanicum), Clove (Eugenia caryophyllus) Ajowan and Amla with 10% starch as a binding agent. Chewable herbal tablets were prepared by wet granulation technique. Prepared tablets were evaluated for weight

variation test, friability, hardness; time required for complete chewing and was found to be within the acceptable limits. DSC and FT-IR spectral studies showed that there was no interaction between the drug and excipients. It can be concluded that the selected formulation of chewable herbal tablets has acceptable physicochemical features and may be considered as herbal medication for cough remedy.

**Hemali Soni and A Patel (2016)[50]** prepared raft forming chewable tablets of Ranitidine hydrochloride by using raft forming agents like pectin, sodium bicarbonate, calcium carbonate for effective treatment of Gastro Esophageal Reflux Disease. The tablets were evaluated for various physicochemical parameters and *in vitro* drug release study. Tablets showed satisfactory results when evaluated for hardness, friability, weight variation, drug content, raft strength and acid neutralizing capacity. Out of all factorial batches (i.e.) PB1 to PB10, PB8 has shown promising results of raft strength as it is sufficient for the prevention of the reflux and fulfilled all the criteria for chewable tablets.

**Mitul Patel *et al.*, (2014)[51]** formulated raft forming chewable tablets of Pantoprazole sodium along with raft forming agents sodium alginate and pectin and antacid (NaHCO3). The tablets were prepared by wet granulation method and evaluated for raft strength, acid neutralization capacity and *in vitro* drug release. The tablets containing appropriate amount of sodium alginate with pectin showed highest raft strength. Raft strength was affected by amount of sodium alginate, pectin and sodium bicarbonate. A $3^2$ full factorial design was used in present study of optimization. Acid neutralization capacity and *in vitro* drug release of all batches was found to be satisfactory. F8 batch was optimized based on maximum raft strength and good acid neutralization capacity and *in vitro* drug release. Stability study of optimized formulation showed that the tablets were stable at accelerated condition and fulfilled all the criteria for chewable tablets.

**Ravi Subhashini *et al.*, (2013)[52]** developed fast dissolving chewable tablets of Domperidone using *Plantago ovata* mucilage as a natural superdisintegrant. The tablets were prepared by direct compression method using microcrystalline cellulose as a directly compressible vehicle. Tablets each containing 10 mg of Domperidone were prepared by employing super-disintegrant at five different concentrations of 2.5%, 5%, 7.5%, 10% and 12.5%. Tablets were evaluated for their physicochemical properties such as weight variation, thickness, hardness, disintegrating time, wetting time and *in vitro* drug release study. Values of angle of repose were found in the range of $18.26^o$ to $19.93^o$ showing that the powder blend was free flowing

and can be used for direct compression. The value of carr's index was in between 10-15% indicating that all the batches of powder blends were having good compressibility. Thickness was observed between 4.1- 4.5 mm, hardness of the tablet was in the range of 3.0-3.9 kg/cm$^2$ and weight loss in the friability was less than 1% in all the cases. Among all the formulations of Domperidone F5 (12.5%) was found to have less disintegration time, wetting time, *in vitro* dispersion time (i.e.) 28 sec, 22 sec and 32 sec respectively and 100% drug release at 12 min. Hence it can be concluded that F5 (12.5%) was found to be better formulation than F1, F2, F3 and F4.

**Fiza F *et al.*, (2014)[53]** developed an effective formulation of Mebendazole chewable tablets by three methods viz non aqueous granulation, aqueous granulation and direct compression. The tablets prepared by these three methods were evaluated for different parameters such as average weight, hardness, carr's index, tapped density, friability, disintegration, content uniformity test and *in vitro* dissolution test. All the parameters were found within the specification. The assay values are within the limit of 90% to 110%. The dissolution profile revealed that tablets prepared by direct compression method showed faster dissolution rate compared to other batches and marketed product. Hence it can be concluded that chewable tablets of Mebendazole could be prepared by direct compression fulfilled all the criteria for chewable tablets.

**Rohan A Khutale *et al.*, (2015)[54]** developed chewable tablets of Ibuprofen by using novel coprocessed excipient consisting of dicalcium phosphate and magnesium stearate, in different ratios. The developed excipients were evaluated for angle of repose, cars index and hausner's ratio in comparison with physical mixture of excipient. The angle of repose of developed excipient was found to be less than 20°, cars index 10-20% and hausners ratio in the range of 1.10 -1.17. Chewable tablets of Ibuprofen were also evaluated for various post compression parameters. Short term stability study (at 40$^0$C/75%RH for 3 months), drug excipients interactions (IR, DSC) were also studied. Among the designed formulations, the formulation (B1) containing (21:0.5 mixture of dicalcium phosphate and magnesium stearate) emerged as the overall best formulation, based on drug release compared to other formulation.

**Pankaj P Amrutkar *et al.*, (2010)[55]** developed taste masked chewable dispersible tablets of Lamotrigine by complexation with Precirol ATO-05. These tablets can be swallowed in the form of dispersion; hence it is suitable dosage form for paediatric and geriatric patients. Drug - Precirol

ATO-05 was prepared in ratio of 1:0.5, 1:1, 1:1.5 and 1:2. The prepared tablets were evaluated for general appearance, content uniformity, hardness, friability, taste evaluation, mouth feel, *in vitro* disintegration time and *in vitro* dissolution studies. Tablets with Precirol ATO-05 have shown good disintegrating features, also the dispersion not shown any bitter taste indicate the capability of Precirol ATO-05 used both as disintegrant and taste masking agent. Almost more than 90 percent of drug was released from the formulation within 1 h. Further formulations were subjected to stability testing for 3 months at 25±5ºC/60±5%RH; 30±5ºC/65±5%RH and 40±5ºC/75±5%RH. Tablets have shown no appreciable changes with respect to taste, disintegration, dissolution profiles and the study concludeds stable Lamotrigine dispersible tablets could be successfully prepared by complexing with Precirol ATO-05.

**Vijaykumar Ghorwade *et al.*, (2011)[56]** prepared Montelukast sodium fast dissolving films by solvent casting method using HPMC as film base with different concentrations of superdisintegrants like microcrystalline cellulose and crospovidone and using PEG 400 as plasticizer. The physicochemical parameters of the fast dissolving films were evaluated. The compatibility of the drug in the formulation was confirmed by IR and DSC studies. Scanning electron microscopy revealed the morphology of the films. *In vitro* dissolution studies and mechanism of drug release was identified. The formulation F2 and F5 with 4% of crospovidone and 10% MCC respectively showed a maximum cumulative percentage drug release of 97.42% and 94.64% at the end of 30 min. The release of drug from the films has followed first-order kinetics. No significant change in the physical parameters, *in vitro* disintegration time and drug content of F2 was observed during storage at $40\pm2^0$C/75±5% RH for 3 months. Hence it can be concluded that 4% crospovidone and 10% MCC with 4% HPMC as a film base was suitable for developing fast dissolving films of Montelukast sodium.

# CHAPTER- 3

# AIM AND PLAN OF WORK

## 3.1 AIM AND OBJECTIVE OF THE WORK

- ✓ The aim of present study is to formulate sugar free Montelukast sodium chewable tablets using various disintegrants and superdisintegrants by direct compression method and to evaluate the formulations for various pharmaceutical parameters and compare with marketed product of Montelukast sodium chewable tablets.
- ✓ Montelukast sodium is used for chronic treatment of asthma and allergic rhinitis. Paediatric, geriatric and bedridden patients show inconvenience in swallowing conventional tablets of Montelukast sodium with lesser amounts of water.
- ✓ Montelukast sodium is basically a tasteless drug. So some patient's does not like to consume the drug orally. Moreover, marketed preparation of Montelukast sodium currently available is not completely devoid of tasteless problem.
- ✓ So the objective of the study is to produce a drug delivery system with better pharmaceutical and therapeutic properties and making the formulation suitable for diabetic and non diabetic patients and minimizing the drawbacks of commercially available conventional Montelukast sodium tablets by formulating sugar free Montelukast sodium chewable tablets thereby improving the patient compliance, convenience in administration and better mouth feel. Also the effectiveness of Montelukast sodium will be improved by the reduction in size that occurs during mastication of drug before swallowing.

# 3.2 PLAN OF WORK

The present work was carried out to formulate sugar free Montelukast sodium chewable tablets and to evaluate the tablets for various pharmaceutical parameters. It was planned to carry out this work as outlined below.

- To carry out the preformulation studies of API such as
  - ✓ Organoleptic properties
  - ✓ Solubility
  - ✓ Drug excipients compatibility study
- To carry out the drug - excipients interaction studies by FT- IR Spectrophotometer.
- To carry out precompression parameters such as
  - ✓ Angle of repose
  - ✓ Bulk density
  - ✓ Tapped density
  - ✓ Compressibility index
  - ✓ Hausner' s ratio
- To formulate sugar free chewable tablets of Montelukast sodium by "Direct compression method".
- To evaluate the compressed tablets for following parameters
  - ✓ Thickness
  - ✓ Hardness
  - ✓ Friability
  - ✓ Weight variation
  - ✓ Wetting time
  - ✓ Water absorption ratio
  - ✓ Taste evaluation
  - ✓ Disintegration time
  - ✓ Assay
  - ✓ *In vitro* dissolution studies
- To perform stability study for the optimized formulation at $25\pm2^0$C/60%±5%RH and $40\pm2^0$C/75%±5%RH for three months.

# CHAPTER - 4

# MATERIALS AND METHODS

## 4.1 LIST OF MATERIALS USED AND MANUFACTURERS

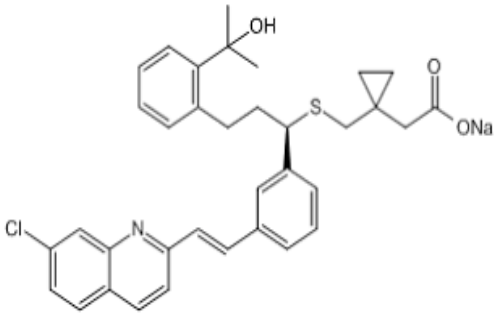
**Table 2: List of Materials used and Manufacturers**

| S. No. | MATERIALS | MANUFACTURERS |
|---|---|---|
| **1** | Montelukast sodium | MetroChem API Pvt. Ltd., Hyderabad, Telangana. |
| **2** | Mannitol anhydrous | Shandong Tunali Pharma, China. |
| **3** | Maize starch | Universal Starch Chemical Alied, Ltd., Mumbai, Maharashtra. |
| **4** | Pregelatinized starch | DFE Pharma, Cuddalore, Tamilnadu. |
| **5** | Sodium starch glycolate | Prachin Chemical Pvt. Ltd., Ahmedabad, Gujarat. |
| **6** | Croscarmellose sodium | Prachin Chemical Pvt. Ltd., Ahmedabad, Gujarat. |
| **7** | Crospovidone | Huangshan Bonsun Pharma Pvt. Ltd., China. |
| **8** | Neo sucralose | Nutra Sweet Company, Jaipur, Rajasthan. |
| **9** | Strawberry powder flavor | Ridhi Sidhi Pharmaceutical Pvt. Ltd., New Delhi. |
| **10** | Iron oxide red | Koel Colours Pvt. Ltd., Mumbai, Maharashtra**.** |
| **11** | Methylparaben | Rasula Pharmaceuticals and Fine Chemicals Pvt. Ltd., Hyderabad, Telangana. |
| **12** | Propylparaben | Rasula Pharmaceuticals and Fine Chemicals Pvt. Ltd., Hyderabad, Telangana. |
| **13** | Magnesium stearate | Accent Microcell Pvt. Ltd., Ahmedabad, Gujarat. |

# 4.2 DRUG PROFILE[57]

**DRUG** : Montelukast Sodium

**STRUCTURAL FORMULA** :




**M OLECULAR FORMULA** : $C_{35}$ $H_{35}$Cl NNa$o_3$S.

**MOLECULAR WEIGHT** 608.169 g/mol.

**CHEMICAL NAME** : Sodium;2-[1-[[(1R)-1-[3-[(E)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(2-hydroxypropan-2-yl) phenyl]propyl]sulfanylmethyl]cyclopropyl]acetate.

**CATEGORY** : Leukotriene receptor antagonists.

**DOSE** : 10 mg OD; Children 2-5 yr: 4mg OD, 6-14yr: 5mg OD.

**DESCRIPTION** : Off white to pale yellow coloured powder.

**SOLUBILITY** : Soluble in water, methanol and ethanol, practically insoluble in acetonitrile.

**MELTING POINT** : 108-110°C.

**MECHANISM OF ACTION[58]**

Montelukast inhibits bronchoconstriction due to antigen challenge. Montelukast is a selective leukotriene receptor antagonist of the cysteinyl leukotriene CysLT $_1$ receptor. The cysteinyl leukotrienes (LTC $_4$, LTD $_4$, LTE $_4$) are products of arachidonic acid metabolism that are released from various cells, including mast cells and eosinophils. They bind to cysteinyl leukotriene receptors (CysLT) found in the human airway. Binding of cysteinyl leukotrienes to leukotriene receptors has been correlated with the pathophysiology of asthma, including airway edema, smooth muscle contraction and altered cellular activity associated with the inflammatory process, factors that contribute to the signs and symptoms of asthma. Montelukast binding to the CysLT $_1$ receptor is high-affinity and selective, preferring the CysLT $_1$ receptor to other pharmacologically important airway receptors, such as the

prostanoid, cholinergic or beta-drenergic receptor. Montelukast inhibits physiologic actions of LTD $_4$ at the CysLT $_1$ receptors, without any agonist activity.

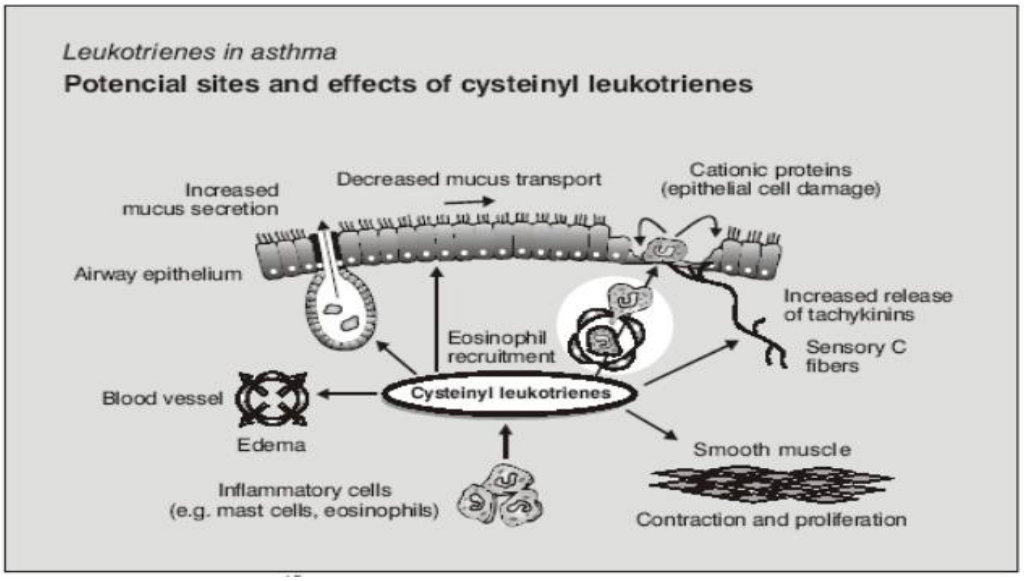



**Fig 2: Potential Sites and Effects of Cysteinyl Leukotrienes**

**PHARMACOKINETICS[59]**

**Absorption**: Rapidly absorbed after oral administration with mean oral bioavailability of 64%. Food doesn't affect absorption of drug.

**Distribution**: Minimally distributed to the tissues with a steady – state volume of distribution of 8 to 11 L. Over 99% is bound to plasma proteins.

**Metabolism**: Extensively metabolized, but plasma levels of metabolites at therapeutic doses are undetectable. *In vitro* studies with human liver microsomes demonstrate metabolism involvement by cytochrome P-450 3A4 and 2c9.

**Excretion**: About 86% of an oral dose is metabolized and excreted in the faeces, indicating drug and its metabolites are excreted almost exclusively in the bile. Half – life is 2 to 5 hours.

**DRUG INTERACTIONS[60]**

Metabolism may be increased with Rifampicin, Phenobarbitol and Phenytoin. Peripheral oedema may occur with Prednisone.

**ADVERSE REACTIONS**

**Central Nervous System** **:** Head ache, dizziness, fatigue, asthenia.

**Gastrointestinal Tract** **:** Dyspepsia, infectious gastroenteritis, abdominal pain.

**Respiratory System** **:** Cough, influenza.

**Skin** **:** Rash.

**Others** **:** Fever, trauma.

**INDICATIONS**

Prophylaxis and chronic treatment of asthma, allergic rhinitis.

**DOSAGE AND ADMINISTRATION[61]**

**Management of chronic asthma:**

**Adult:** 10 mg once daily in the evening.

**Child:** 2-5 yr: 4mg daily; 6-14 yr: 5mg daily; 15 yr: 10 mg once daily.

All doses to be taken in the evening.

**CONTRAINDICATIONS:**

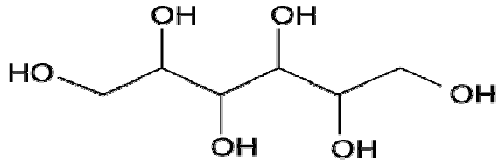
Contraindicated in patients with hypersensitivity to drug or its components. Also contraindicated in patients with acute asthmatic attacks or status asthmatics. Although airway function is improved in patients with known aspirin hypersensitivity, these patients should avoid aspirin and NSAID[S].

**MARKETED PRODUCTS:**

Montelast (tab), Monti (tab), Romilast(tab), Romilast (oral granules), Symkast(tab),Telekast (tab)Zmont theo (combination tab), Lukalov-M (syrup), Levontel (syrup).

## 4.3. EXCIPIENTS PROFILE

### 4.3.1 MANNITOL[62, 63]

| | | |
|---|---|---|
| **NON PROPRIETARY NAMES** | : | BP: Mannitol.<br>JP: D-Mannitol.<br>PhEur: Mannitol.<br>USP: Mannitol. |
| **SYNONYMS** | : | Cordycepic acid, emprove; manna sugar; D-mannite; mannite; mannitolum; mannogem; Pearlitol. |
| **CHEMICAL NAME** | : | D-Mannitol. |
| **EMPIRICAL FORMULA** | : | $C_6H_{14}O_6$ |
| **MOLECULAR STRUCTURE** | : |  |
| **MOLECULAR WEIGHT** | : | 182.17 g/mol. |
| **MELTING POINT** | : | 166–168°C. |
| **SOLUBILITY** | : | Soluble in alkalis and practically insoluble in ether. |
| **DESCRIPTION** | : | Mannitol occurs as a white, odorless, crystalline powder or free- flowing granules. |
| **FUNCTIONAL CATEGORY** | : | Diluent; plasticizer; sweetening agent; tablet and capsule diluents, tonicity agent. |
| **APPLICATIONS** | : | Mannitol is widely used in pharmaceutical formulations and food products. Mannitol may be used in direct-compression tablet applications, for which the granular and spray dried forms are available or in wet granulations. |
| **STABILITY AND STORAGE CONDITIONS** | : | Mannitol is stable in the dry state and in aqueous solutions. The bulk material should be stored in a well-closed container in a cool, dry place. |

**INCOMPATIBILITIES** **:** Mannitol solution, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride. Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic.

## 4.3.2 STARCH[62]

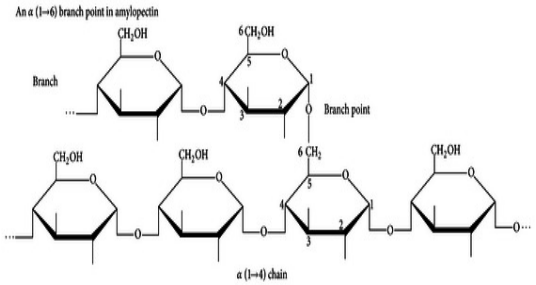
**NON PROPRIETARY NAMES** : BP: Maize starch
JP: Corn starch
PhEur: Pea starch
USP-NF: Corn starch

**SYNONYMS** : Amido; amidon; amilo; amylum.

**CHEMICAL NAME** : Starch.

**EMPIRICAL FORMULA** : $C_6H_{10}O_5n$

**MOLECULAR STRUCTURE** :




**MOLECULAR WEIGHT** : 164.1406 g/mol.

**MELTING POINT** : 256°C- 286°C.

**SOLUBILITY** : Practically insoluble in organic solvents. Slightly soluble to soluble in cold water, depending upon the degree of pregelatinization.

**DESCRIPTION** : Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.

**FUNCTIONAL CATEGORY** : Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

**APPLICATIONS** : Starch is primarily used in oral solid dosage formulations as a binder, diluent and disintegrant.

**STABILITY AND STORAGE CONDITIONS** : Pregelatinized starch is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.

**INCOMPATIBILITIES** **:** Starch is incompatible with strong oxidizing substance. Colored inclusion compounds are formed with Iodine.

## 4.3.3. SODIUM STARCH GLYCOLATE[63, 64]

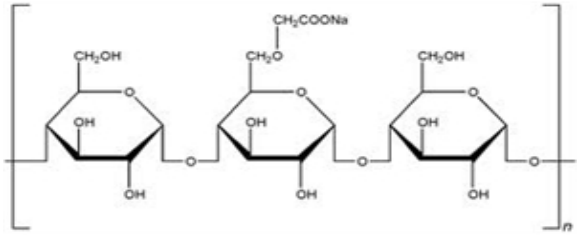
**NON PROPRIETARY NAMES** : BP: Sodium starch glycolate
PhEur: Sodium starch glycolate
USP-NF: Sodium starch glycolate

**SYNONYMS** : Carboxymethyl starch, sodium salt, Explosol, Explotab, Glycolys, Primojel, starch carboxymethyl ether.

**CHEMICAL NAME** : Sodium carboxymethyl starch.

**EMPIRICAL FORMULA** : $C_2H_4O_3$.

**MOLECULAR STRUCTURE** :




**MOLECULAR WEIGHT** : 98.033 g/mol.

**MELTING POINT** Does not melt but chars at 200°C.

**SOLUBILITY** : Sparingly soluble in ethanol (95%), practically insoluble in water.

**DESCRIPTION** : Sodium starch glycolate is a white or almost white, hygroscopic free-flowing powder.

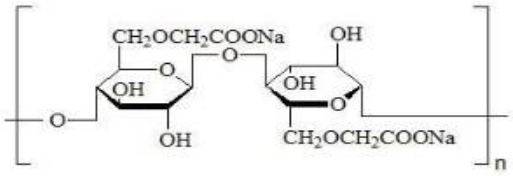
**FUNCTIONAL CATEGORY** : Tablet and capsule disintegrant.

**APPLICATIONS** : Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet granulation processes.

**STABILITY AND STORAGE CONDITIONS** : Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable although very hygroscopic, and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

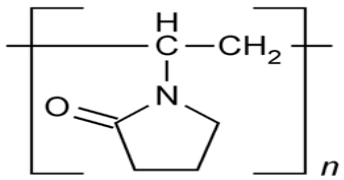
**INCOMPATIBILITIES** : Sodium starch glycolate is incompatible with ascorbic acid.

## 4.3.4 CROSCARMELLOSE SODIUM[65]

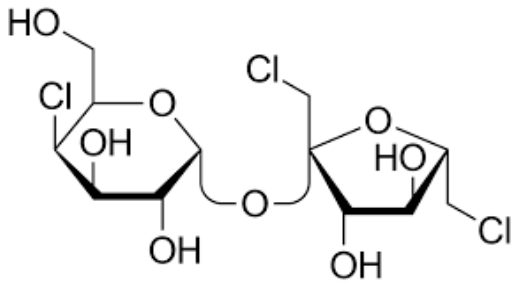
| | | |
|---|---|---|
| **NON PROPRIETARY NAMES** | : | BP: Croscarmellose sodium<br>JP: Croscarmellose sodium<br>PhEur: Croscarmellose sodium<br>USP-NF: Croscarmellose sodium |
| **SYNONYMS** | : | Ac-Di-Sol, carmellosum natricum conexum, crosslinked carboxymethylcellulose sodium, pharmacel XL, primellose, solutab, vivasol. |
| **CHEMICAL NAME** | : | Cellulose, carboxymethyl ether, sodium salt. |
| **EMPIRICAL FORMULA** | : | $C_{12}H_{30}NA_8O_{27}$ |
| **MOLECULAR STRUCTURE** | : |  |
| **MOLECULAR WEIGHT** | : | 90,000-700,000. |
| **MELTING POINT** | : | More than 205°C |
| **SOLUBILITY** | : | Insoluble in water, although croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene. |
| **DESCRIPTION** | : | Croscarmellose sodium occurs as an odorless, white or greyish white powder. |
| **FUNCTIONAL CATEGORY** | : | Tablet and capsule disintegrant. |
| **APPLICATIONS** | : | Croscarmellose sodium is used in oral pharmaceutical formulations as a superdisintegrant. |
| **STABILITY AND STORAGE CONDITIONS** | : | Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 38°C for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place. |

**INCOMPATIBILITIES** **:** The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

## 4.3.5 CROSPOVIDONE[62]

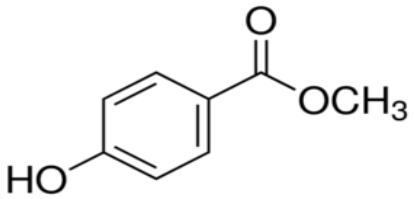
| | | |
|---|---|---|
| **NON PROPRIETARY NAMES** | : | BP: Crospovidone<br>PhEur: Crospovidone<br>USP-NF: Crospovidone |
| **SYNONYMS** | : | Crospovidonum, Crospopharm, crosslinked povidone, kollidon CL, kollidon CL-M |
| **CHEMICAL NAME** | : | Povinyl-2-pyrrolidinone homopolymer,<br>1-Ethenyl-2-pyrrolidinone homopolymer. |
| **EMPIRICAL FORMULA** | : | $C_6H_9NO$ |
| **MOLECULAR STRUCTURE** | : |  |
| **MOLECULAR WEIGHT** | : | 40,000 g\mol. |
| **MELTING POINT** | : | 150°C |
| **SOLUBILITY** | : | Practically insoluble in water and most common organic solvents. |
| **DESCRIPTION** | : | Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odorless or nearly odorless powder. |
| **FUNCTIONAL CATEGORY** | : | Tablet disintegrant. |
| **APPLICATIONS** | : | Crospovidone is a solubility enhancer**.** |
| **STABILITY AND STORAGE CONDITIONS** | : | Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place. |
| **INCOMPATIBILITIES** | : | Crospovidone is incompatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adduct with some materials. |

## 4.3.6 NEO SUCRALOSE[62, 66]

| | | |
|---|---|---|
| **NON PROPRIETARY NAMES** | : | USP-NF: Sucralose. |
| **SYNONYMS** | : | Splenda, sucralose, sucralosum, sucraplus. |
| **CHEMICAL NAME** | : | 1,6-Dichloro-1,6-dideoxy D-fructofuranosyl-4-chloro-4-deoxya-D-galactopyranoside . |
| **EMPIRICAL FORMULA** | : | $C_{12}H_{19}C_{l3}O_8$ |
| **MOLECULAR STRUCTURE** | : |  |
| **MOLECULAR WEIGHT** | : | 397.64 g/mol. |
| **MELTING POINT** | : | 130°C. |
| **SOLUBILITY** | : | Freely soluble in ethanol (95%), methanol and water, slightly soluble in ethyl acetate. |
| **DESCRIPTION** | : | Sucralose is a white to off-white colored, free-flowing, crystalline powder. |
| **FUNCTIONAL CATEGORY** | : | Sweetening agent. |
| **APPLICATIONS** | : | Sucralose is used as a sweetening agent in beverages, foods and pharmaceutical applications. It has a sweetening power approximately 300–1000 times that of sucrose and has no aftertaste. |
| **STABILITY AND STORAGE CONDITIONS** | : | Sucralose should be stored in a well-closed container in a cool, dry place, at a temperature not exceeding 20°C. Sucralose, when heated at elevated temperatures, may break down with the release of carbon dioxide, carbon monoxide and minor amounts of hydrogen chloride. |

**INCOMPATIBILITIES** : Sucralose may be contaminated with traces of heavy metals, which can lead to incompatibility with active ingredients e.g. Ascorbic acid. It may also be contaminated with sulfite from the refining process.

## 4.3.7 METHYL PARABEN[62]

| | | |
|---|---|---|
| **NON PROPRIETARY NAMES** | : | BP: Methyl hydroxybenzoate<br>JP: Methyl parahydroxybenzoate<br>PhEur: Methyl parahydroxybenzoate<br>USP-NF: Methylparaben |
| **SYNONYMS** | : | 4-Hydroxybenzoic acid methyl ester, metagin. |
| **CHEMICAL NAME** | : | Methyl-4-hydroxybenzoate. |
| **EMPIRICAL FORMULA** | : | $C_8H_8O_3$ |
| **MOLECULAR STRUCTURE** | : |  |
| **MOLECULAR WEIGHT** | : | 152.15 g/mol. |
| **MELTING POINT** | : | 125-128°C. |
| **SOLUBILITY** | : | Soluble in acetone, alcohol and mineral oil, water, when heated. |
| **DESCRIPTION** | : | Methylparaben occurs as colorless crystals or a white crystalline powder. It is odorless or almost odorless and has a slight burning taste. |
| **FUNCTIONAL CATEGORY** | | Antimicrobial preservative. |
| **APPLICATIONS** | : | Methylparaben is widely used as an antimicrobial preservative in cosmetics, food products and pharmaceutical formulations. |
| **STABILITY AND STORAGE CONDITIONS** | : | Aqueous solutions of methylparaben at pH 3–6 may be sterilized by autoclaving at 121°C for 20 minutes, without decomposition. Methylparaben should be stored in a well closed container in a cool and dry place. |
| **INCOMPATIBILITIES** | : | Incompatibilities with other substances, such as bentonite, magnesium trisilicate, talc, tragacanth, sodium alginate, essential oils, sorbitol and Atropine, have been reported. It also reacts with various sugars and related sugar alcohols. |

## 4.3.8 PROPYL PARABEN[62, 67]

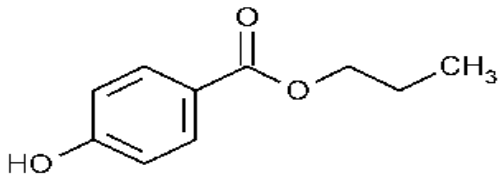
**NON PROPRIETARY NAMES** : BP: Propyl hydroxybenzoate
JP: Propyl parahydroxybenzoate
PhEur: Propyl parahydroxybenzoate
USP-NF: Propylparaben.

**SYNONYMS** : 4-Hydroxybenzoic acid propylester, nipasol, propagin, propyl aseptoform, propyl butex, propyl chemosept.

**CHEMICAL NAME** : Propyl 4-hydroxybenzoate.

**EMPIRICAL FORMULA** : $C_{10}H_{12}O_3$

**MOLECULAR STRUCTURE** :




**MOLECULAR WEIGHT** : 180.20 g/mol.

**MELTING POINT** : 96 - 99°C.

**SOLUBILITY** : Soluble in acetone, alcohol and mineral oil, water, when heated.

**DESCRIPTION** : Propylparaben occurs as a white, crystalline, odorless and tasteless powder.

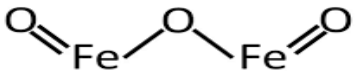
**FUNCTIONAL CATEGORY** : Antimicrobial preservative.

**APPLICATIONS** : Propylparaben is widely used as an antimicrobial preservative in cosmetics, food products and pharmaceutical formulations. It may be used alone, in combination with other paraben esters or with other antimicrobial agents. It is one of the most frequently used preservatives in cosmetics.

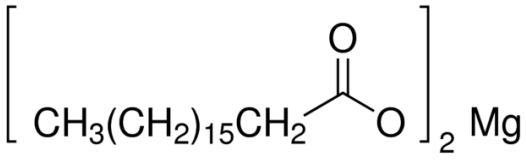
**STABILITY AND STORAGE CONDITIONS** : Aqueous propylparaben solutions at pH 3-6 can be sterilized by autoclaving, without decomposition. At pH 3–6, aqueous solutions are stable (less than 10% decomposition) for upto 4 years at room temperature, while solutions at pH 8 or above undergo rapid hydrolysis.

**INCOMPATIBILITIES** **:** The antimicrobial activity of propylparaben is reduced considerably in the presence of nonionic surfactants as a result of micellization. Absorption of propylparaben by plastics has been reported, with the amount absorbed dependent upon the type of plastic and the vehicle. Propylparaben is discolored in the presence of iron and is subject to hydrolysis by weak alkalis and strong acids.

## 4.3.9 IRON OXIDE RED[62, 68]

| | | |
|---|---|---|
| **NON PROPRIETARY NAMES** | **:** | Iron oxides. |
| **SYNONYMS** | **:** | Anhydrous ferric oxide, anhydrous iron, ferroxide, hematite, pigment red, red ferric oxide, sicovit. |
| **CHEMICAL NAME** | **:** | Iron oxide red. |
| **EMPIRICAL FORMULA** | **:** | $Fe_2O_3$. |
| **MOLECULAR STRUCTURE** | **:** |  |
| **MOLECULAR WEIGHT** | **:** | 159.70 g\mol. |
| **MELTING POINT** | **:** | 1,565°C. |
| **SOLUBILITY** | **:** | Soluble in mineral acids, insoluble in water. |
| **DESCRIPTION** | **:** | Iron oxides occur as yellow, red, black or brown powder. The color depends on the particle size, shape and crystal structure. |
| **FUNCTIONAL CATEGORY** | **:** | Colorant. |
| **APPLICATIONS** | **:** | Iron oxides are widely used in cosmetics, foods and pharmaceutical applications as colorants and UV absorbers. As inorganic colorants they are becoming of increasing importance as a result of the limitations affecting some synthetic organic dyestuffs. |
| **STABILITY AND STORAGE CONDITIONS** | **:** | Iron oxides should be stored in well-closed containers in a cool, dry place. |
| **INCOMPATIBILITIES** | **:** | Iron oxides incompatible with comman organic acids, mineral acids and oxidizing agents. |

## 4.3.10 MAGNESIUM STEARATE[62]

| | | |
|---|---|---|
| **NON PROPRIETARY NAMES** | : | BP: Magnesium stearate<br>JP: Magnesium stearate<br>PhEur: Magnesium stearate<br>USP-NF: Magnesium stearate |
| **SYNONYMS** | : | Dibasic magnesium stearate, magnesium distearate, magnesium stearas, magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid. |
| **CHEMICAL NAME** | : | Octadecanoic acid magnesium salt. |
| **EMPIRICAL FORMULA** | : | $C_{36}H_{70}MgO_4$ |
| **MOLECULAR STRUCTURE** | : |  |
| **MOLECULAR WEIGHT** | : | 591.24 g\mol. |
| **MELTING POINT** | : | 88°C. |
| **SOLUBILITY** | : | Practically insoluble in ethanol, ether and water, slightly soluble in warm benzene and warm ethanol (95%). |
| **DESCRIPTION** | : | Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder having a faint odor and a characteristic taste. The powder is greasy to touch and readily adheres to the skin. |
| **FUNCTIONAL CATEGORY** | : | Tablet and capsule lubricant. |
| **APPLICATIONS** | : | Magnesium stearate is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams. |
| **STABILITY AND STORAGE CONDITIONS** | : | Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place. |

**INCOMPATIBILITIES** : Incompatible with strong acids, alkalis and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate is also incompatible with Aspirin, some vitamins and most alkaloidal salts.

## 4.4. INSTRUMENTS USED AND MANUFACTURERS

**Table: 3 List of Instruments Used and Manufacturers**

| S. No. | Instruments | Manufacturers |
|---|---|---|
| 1 | Single pan electronic balance | Sartorius AG, Germany. |
| 2 | 12 Station D\B tooling compression machine | Fluidpack, Ahmedabad. |
| 3 | Vernier caliper | Mitutoyo Corporation, Japan. |
| 4 | Dissolution apparatus | Electro Lab India Pvt. Ltd., Mumbai. |
| 5 | Hardness tester | Campbell Electronics, Mumbai. |
| 6 | Friability apparatus | Electro Lab India Pvt. Ltd., Mumbai. |
| 7 | Standard sieves | Jayant Scientific Industries, Mumbai. |
| 8 | Disintegration apparatus | Electro Lab India Pvt. Ltd., Mumbai. |
| 9 | FT-IR spectrophotometer | Shimadzu, Japan. |
| 10 | HPLC | Water Corporation, USA. |
| 11 | Stability chamber | Labtop Instruments Pvt. Ltd., Mumbai. |
| 12 | Blister packing machine | Elmach packages India Pvt. Ltd., Mumbai. |
| 13 | UV | UV Spectrum-1800 |

# 4.5 METHODOLOGY

### 4.5.1 PREFORMULATION STUDIES[69]

After drug discovery, with a background of physical, chemical and derived powdered properties of the drug molecule, the drug has to be formulated in the form that can suitably be administered. The first phase of physico-chemical data collection on drug substances, evaluating potential salts thereof and excipient suitability, prior to formulation, is known as preformulation. Preformulation is the interface between new drug entity and formulation development. It also provides road map for formulation development. Preformulation involves the application of biopharmaceutical principles to the physico-chemical parameters of the drug with the goal of designing an optimum drug delivery system. Characterization of the drug molecule is the very important step at the preformulation phase of product development. Therefore, Preformulation studies are an important tool early in the development of both API and drug products. The interaction between the drug and the excipients used in the formulation are generally included in the study, resulting in intelligent selection of excipients. The preliminary drug degradation profiles are included in the study to guide the formulation of a stable product.

#### 4.5.1.1 ORGANOLEPTIC PROPERTIES

The organoleptic properties like color, odor and taste of API were evaluated.

a. **Color:** A small amount of Montelukast sodium was taken in a butter paper and viewed in a well – illuminated place.
b. **Taste and odor:** Very less amount of Montelukast sodium was used to assess the taste with help of tongue as well as smelled to get odor.

### 4.5.1.2 SOLUBILITY TEST [70]

Solubility of Montelukast sodium in water, ethanol, methanol was determined by using sonicator at room temperature. Approximate solubility of drugs as per I.P was mentioned in Table 4.

**Table: 4 Solubility Specifications**

| Solubility | Approximate Volume of Solvent in ml per gm of Solute |
|---|---|
| Very soluble | less than 1 |
| Freely soluble | 1 to 10 |
| Soluble | 10 to 30 |
| Sparingly soluble | 30 to 100 |
| Slightly soluble | 100 to 1000 |
| Very slightly soluble | 1000 to 10000 |
| Practically insoluble | More than 10000 |

### 4.5.1.3 DRUG - EXCIPIENTS COMPATIBILITY STUDIES [71]

Compatibility studies were performed by preparing blend of different excipients with drug and stored at room temperature for one month. The blends were evaluated for every 15 days for changes like caking, liquefaction, discoloration and odor formation. The drug excipients compatibility profiles were shown in Table 5.

**Table: 5 Drug - Excipients Compatibility Protocol**

| S. No. | Drug and Excipients | Ratio (Drug:Excipients) |
|---|---|---|
| 1. | Montelukast sodium | 1 |
| 2. | Montelukast sodium + Mannitol anhydrous | 1:1 |
| 3. | Montelukast sodium + Maize starch | 1:1 |
| 4. | Montelukast sodium + Pregelatinized starch | 1:1 |
| 5. | Montelukast sodium + Sodium starch glycolate | 1:1 |
| 6. | Montelukast sodium + Croscarmellose sodium | 1:1 |
| 7. | Montelukast sodium + Crospovidone | 1:1 |
| 8. | Montelukast sodium + Neo sucralose | 1:1 |
| 9. | Montelukast sodium + Strawberry powder flavor | 1:0.5 |
| 10. | Montelukast sodium + Iron oxide red | 1:0.5 |
| 11. | Montelukast sodium + Methylparaben | 1:1 |
| 12. | Montelukast sodium + Propylparaben | 1:1 |
| 13. | Montelukast sodium + Magnesium stearate | 1:1 |

### 4.5.2 FT – IR SPECTRAL ANALYSIS [72]

Drug – excipients mixture of 1:1 ratio were accurately weighed and compatibility of freshly prepared mixtures was determined by FT-IR spectroscopy. FT-IR spectra of drug, excipient and the physical mixture of drug and excipients were recorded on a Fourier-transform infrared spectrophotometer (Shimadzu FT-IR, Japan) in the range of 4500 – 400 $cm^{-1}$ and observed for any interaction between drug and excipients.

### 4.5.3 EVALUATION OF PRECOMPRESSION PARAMETERS

#### 4.5.3.1 MICROMERITIC PROPERTIES

##### 4.5.3.1.1 ANGLE OF REPOSE[73]

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

**Method:**

The angle of repose was determined by funnel method. The funnel was fixed at a particular height 'h' on a burette stand. A graph paper was placed below the funnel on the table. The powder blend whose angle of repose is to be determined was passed slowly through the funnel, until it forms a pile. Further addition of powder blend was stopped as soon as the pile touches the tip of the funnel. Circumference of powder blend was drawn without disturbing the pile and height of pile was measured. The radius of the pile "r" and height of pile "h" were noted. Angle of repose is determined using the following formula.

$$\theta = \tan^{-1} (h/r)$$

Where,

$\theta$ = Angle of repose

h = Height of the pile

r = Radius of the pile

Flow properties and corresponding angle of repose as per USP was listed in Table 6.

**Table: 6 Flow Properties and Corresponding Angle of Repose as per USP**

| S. No. | Type of Flow | Angle of Repose (Ɵ) |
|---|---|---|
| 1. | Excellent | 25 – 30 |
| 2. | Good | 31 – 35 |
| 3. | Fair | 36 – 40 |
| 4. | Passable | 41- 45 |
| 5. | Poor | 46 – 55 |
| 6. | Very poor | 56 – 65 |
| 7. | Extremely poor | > 66 |

**4.5.3.1.2 BULK DENSITY [74]**

Accurate quantity of weighed powder blend was transferred into a 50ml measuring cylinder without any tapping during transfer and the volume occupied by the powder blend was measured. Bulk density (Db) was determined by using formula.

$$D_b = m/ v_0$$

Where,

$D_b$ = Bulk density

m = Mass of the blend in gm

$v_0$ = Untapped volume

**4.5.3.1.3 TAPPED DENSITY [75]**

Tapped density is determined by introducing the known quantity of powder blend into a graduated cylinder and the cylinder was mechanically tapped by placing on the bulk density apparatus. The volume was measured by tapping the powder blend for 500 times. Then the tapping was done for 750 times and the tapped volume was noted. The tapped density was calculated by using the formula.

$$D_t = m/v_t$$

Where,

$D_t$ = Tapped density,

m = Mass of blend in gm

$v_t$ = Tapped density

### 4.5.3.1.4 MEASUREMENT OF POWDER COMPRESSIBILITY [76]

**A. Compressibility Index**

The word compressibility is the ability to reduce the volume under pressure. The compressibility index of powder blend was determined by the carr's compressibility index. It is used as an indication of the flowability of a powder. A compressibility index greater than 25 is an indication of poor flowability and below 15 indicates good flowability.

$$\textbf{Compressibility index} = \frac{(\textbf{Tapped density} - \textbf{Bulk density})}{\textbf{Tapped density}} \times 100$$

**B. Hausner's Ratio**

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ideal value should be 1.2–1.5. Hausner's ratio was determined by the ratio of tapped density and bulk density. The scale of flowability was shown in Table 7.

$$\textbf{Hausner's ratio} = \frac{\textbf{Tapped density}}{\textbf{Bulk density}}$$

**Table: 7 Scale of Flowability**

| Compressibility Index (%) | Flow Character | Hausner's Ratio |
|---|---|---|
| 01 – 10 | Excellent | 1.00 – 1.11 |
| 11 – 15 | Good | 1.12 – 1.18 |
| 16 – 20 | Fair | 1.19 – 1.25 |
| 21 – 25 | Passable | 1.26 – 1.34 |
| 26 – 31 | Poor | 1.35 – 1.45 |
| 32 – 37 | Very poor | 1.46 – 1.59 |

### 4.5.4 FORMULATION OF MONTELUKAST SODIUM CHEWABLE TABLETS BY DIRECT COMPRESSION METHOD[77]

Chewable tablets of Montelukast sodium were prepared by direct compression method as per the composition shown in Table 8. Five formulations (F-I to F-V) were prepared by direct compression method.

**DIRECT COMPRESSION METHOD**

**Sieving**

The active ingredient was passed through the sieve # 40. The other ingredients given in the formulation table were passed separately through the same sieve.

**Dry mixing**

All the materials (including the active ingredient) were weighed and taken in a poly bag and mixed for 10 minutes.

**Lubrication**

The magnesium stearate was passed through the sieve # 60 and mixed together with the powder mixture in a polybag for 5 minutes to get a uniform blend.

**Compression**

Finally, the powder mixture was compressed into tablets using rotary tablet compression machine of punch size 7.14mm to prepare tablets each weighing 150mg.

**Packing**

The prepared tablets were packed by PVC- Alu Blister packing.

**FORMULATION FLOW CHART OF DIRECT COMPRESSION METHOD**

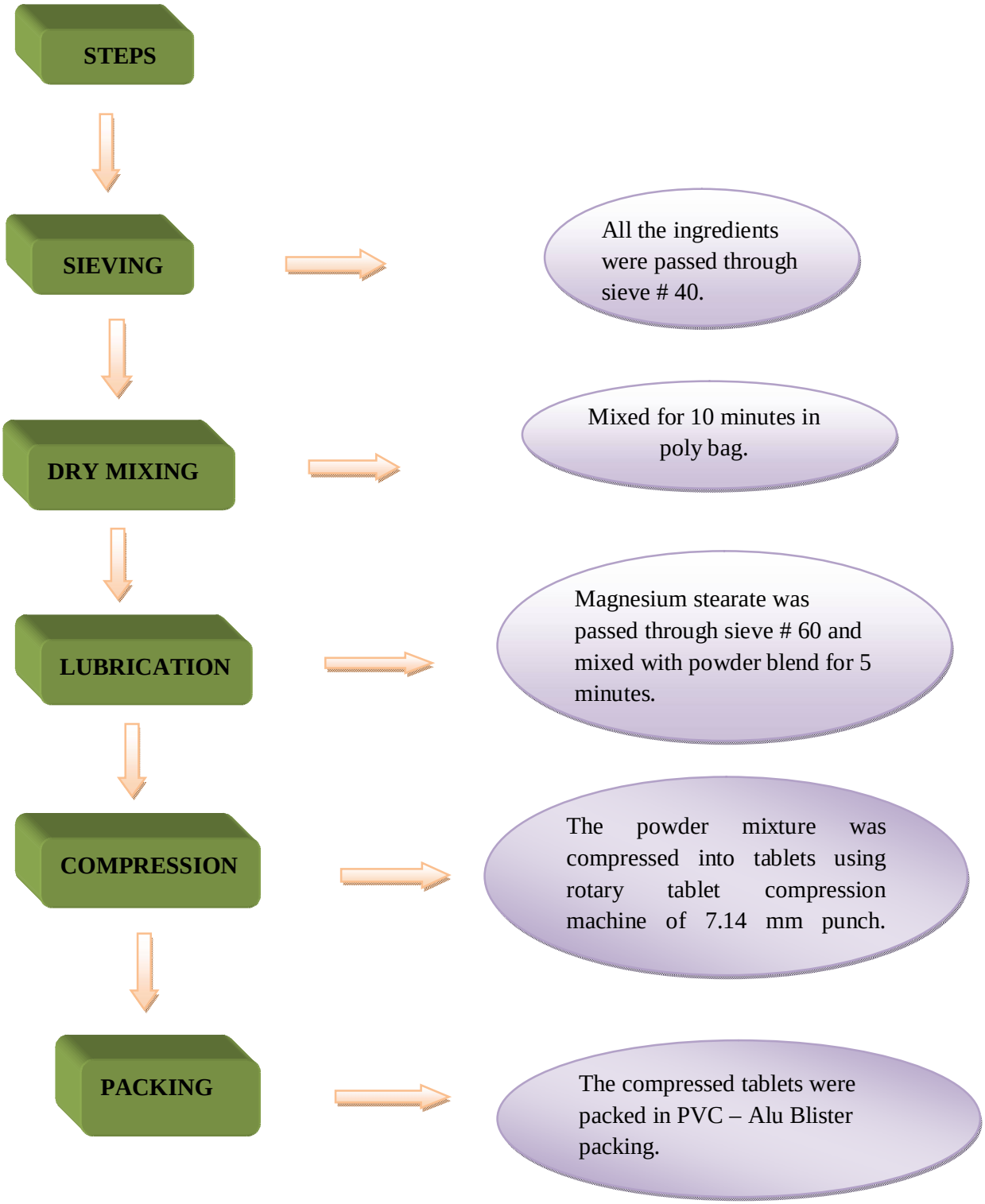


**Table: 8 Composition of Montelukast sodium Chewable Tablets**

| Ingredients | Quantity per Tablet (mg) | | | | |
|---|---|---|---|---|---|
| | Formulation Code | | | | |
| | **F-I** | **F-II** | **F-III** | **F-IV** | **F-V** |
| Montelukast sodium | 5.00 | 5.00 | 5.00 | 5.00 | 5.00 |
| Mannitol anhydrous | 124.20 | 124.20 | 124.20 | 124.20 | 124.20 |
| Maize starch | 15.00 | - | - | - | - |
| Pregelatinized starch | - | 15.00 | - | - | - |
| Sodium starch glycolate | - | - | 15.00 | - | - |
| Croscarmellose sodium | - | - | - | 15.00 | - |
| Crospovidone | - | - | - | - | 15.00 |
| Neo sucralose | 1.50 | 1.50 | 1.50 | 1.50 | 1.50 |
| Strawberry powder flavor | 0.80 | 0.80 | 0.80 | 0.80 | 0.80 |
| Iron oxide red | 0.20 | 0.20 | 0.20 | 0.20 | 0.20 |
| Methylparaben | 1.50 | 1.50 | 1.50 | 1.50 | 1.50 |
| Propylparaben | 0.30 | 0.30 | 0.30 | 0.30 | 0.30 |
| Magnesium stearate | 1.50 | 1.50 | 1.50 | 1.50 | 1.50 |
| **Weight of each tablet (mg)** | **150.00** | **150.00** | **150.00** | **150.00** | **150.00** |

## 4.5.5 POST COMPRESSION PARAMETERS

The compressed tablets were evaluated for the following parameters.

### 4.5.5.1 GENERAL APPEARANCE

The compressed tablets were examined under a biconvex lens for surface cracks, depression and pinholes.

### 4.5.5.2 THICKNESS [78]

The diameter and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by screw gauge. Thickness values were expressed in millimeter.

The thickness was measured by placing the tablet between two arms of the vernier caliper. Five tablets were taken and their thickness was measured.

### 4.5.5.3 HARDNESS TEST OR CRUSHING STRENGTH[79]

The tablet requires a certain amount of strength or hardness, to withstand mechanical shocks of handling during its manufacture, packaging and transport. In addition tablets should be able to withstand reasonable abuse when in the hands of the consumer. Adequate tablet hardness and resistance to powdering and friability are necessary requisites for consumer acceptance.

Hardness of the tablet is defined as the force required in breaking a tablet in a diametric compression test. Hence hardness is sometimes referred to as “crushing strength”. It was measured using Monsanto tablet hardness tester. The values were expressed in $kg/cm^2$. In this test, a tablet was placed between two anvils, force was applied to the anvils and the crushing strength that just causes the tablet to break is recorded.

### 4.5.5.4 WEIGHT VARIATION TEST [80]

Weigh individually 20 tablets and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation given in Table 9 and none should deviate by more than twice that percentage limit. The uniformity of weight and percentage deviation of tablets as per IP were presented in Table 9.

**Table: 9 Uniformity of Weight and Percentage Deviation**

| S.No. | Average Weight of Tablet (mg) | Percentage Deviation (%) |
|---|---|---|
| 1. | 130 mg or less | ± 10% |
| 2. | More than 130 mg or less than 324 mg | ± 7.5% |
| 3. | 324 mg or more | ± 5% |

The percentage deviation of the tablets were calculated by the formula,

$$\textbf{Percentage deviation} = \frac{(\textbf{Weight of tablet (mg)} - \textbf{Average weight of tablet (mg)})}{\textbf{Average weight of tablet (mg)}} \times 100$$

### 4.5.5.5 FRIABILITY [81]

The friability test of tablets was determined by using Roche friabilator. Ten tablets were dusted and weighed on the analytical balance. The tablets were placed in the drum of the friability tester and rotated for 100 times at 25 RPM for 4 minutes. The tablets were de dusted and reweighed. The percentage friability of the tablets were calculated by the formula.

$$\textbf{Percentage Friability (\%)} = \frac{\textbf{Initial weight} - \textbf{Final weight}}{\textbf{Initial weight}} \times 100$$

### 4.5.5.6 TASTE EVALUATION (SENSORY EVALUATION) [82]

Sensory evaluation is defined as a scientific disciplines used to measure, analyze and interpret reaction to those characteristic of material as they are received by the senses of sight, smell, taste, touch and hearing.

The taste evaluation was done by taste panels. The method chosen was ranking test and for this purpose 10 human volunteer was selected. The dispersion of pure drug and trial formulations were given to the panelists. The intensity of bitterness was asked from panelists.

### 4.5.5.7 DISINTEGRATION TIME [83]

For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution and the first important step towards this condition is usually the break-up of the tablet; a process known as disintegration.

Place 1 tablet in each of these six tubes of the basket and one disk was added to each tube. Operate the disintegration apparatus using 900 ml of distilled water at $37^0 \pm 2^0$C. The time taken in seconds for complete disintegration of the tablets with no palpable mass remaining in the apparatus was measured.

### 4.5.5.8 WETTING TIME AND WATER ABSORPTION RATIO [84]

A piece of tissue paper folded twice was placed in a small petridish (internal diameter = 6.5cm) containing 6 ml of water. A preweighed tablet was placed on the surface of the paper and the time required for complete wetting was then measured. The time required for the water to reach upper surface of the tablet was noted as the wetting time. The water absorption ratio (R) was determined using the following equation.

$$R = \frac{Wa - Wb}{Wb} \times 100$$

Where,

Wa - Weight of tablet before wetting.

Wb - Weight of tablet after wetting.

### 4.5.5.9 ASSAY OF MONTELUKAST SODIUM BY HPLC METHOD [85]

**Chromatographic Conditions**

| | | |
|---|---|---|
| Column | : | Stainless steel column 15 cm × 4.6 mm. |
| Mobile phase | : | 22 ml buffer solution, 78 ml Methanol. |
| Buffer | : | Dissolve 3.85 gm of ammonium acetate in 1000 ml of water and add 1ml of triethyl amine. Adjust the pH to 5.5 with glacial acetic acid. |
| Flow rate | : | 1.5 ml per minute. |
| Injection volume | : | 10 µl. |
| Wave length | : | 240 nm. |
| Temperature | : | 40°C. |

**Preparation of Mobile Phase**

Buffer and Methanol were mixed in the ratio of 22:78. The pH of the mobile phase was adjusted to 5.5.

**Preparation of Standard Solution**

0.005% w/v solution of Montelukast reference standard in methanol.

**Preparation of Sample Solution**

20 tablets were weighed and powdered. The powder equivalent to 50mg of Montelukast was dissolved in methanol. 1.0 ml of this solution was diluted to 10 ml with methanol.

**Sample Injection Procedure**

10 µl of filtered sample solution and standard solution were separately injected into HPLC system. The chromatogram was recorded and responses were measured for major peaks.

The content of Montelukast in the powder mixture was calculated by using the following equation,

$$\text{Content of Montelukast sodium} = \frac{Sample\ area}{Standard\ area} \times \frac{Standard\ weight}{Sample\ weight} \times \frac{P}{100} \times Avg.Wt$$

Where,

P = Purity of Montelukast sodium

Avg. Wt = Average weight in mg

### 4.5.5.10 *IN VITRO* DISSOLUTION STUDIES [86]

**Dissolution Parameters**

| | | |
|---|---|---|
| Apparatus | : | USP Dissolution apparatus, Type II (Paddle). |
| Medium | : | 900ml of distilled water with 0.5% SLS. |
| RPM | : | 50. |
| Temperature | : | 37℃ ± 0.5℃. |
| Sampling interval | : | 5, 10, 15, 20, 25 and 30. |
| Sample withdrawn | : | 5 ml. |
| Wavelength | : | 350 nm. |
| Instrument | : | UV spectrophotometer. |

**Preparation of 0.5% Sodium lauryl sulphate Solution**

Place 5 gm of sodium lauryl sulphate into the 1000 ml volumetric flask and the volume was made up with de - mineralized water.

**Procedure**

The *in-vitro* dissolution studies of Montelukast sodium chewable tablets were performed using dissolution apparatus USP Type II (paddle). The volume of dissolution medium (distilled water with 0.5% SLS solution) used was 900 ml and the temperature was maintained at 37±0.5˚C. The speed of the paddle was set at 50 rpm. One tablet was placed in each jar of dissolution apparatus. 5ml of sample from each jar was withdrawn at every 5 minutes interval upto 30 minutes and same volume of dissolution medium was replaced to each dissolution jar, so that volume of dissolution medium was maintained to 900 ml. The sample was filtered and diluted with dissolution medium and the amount of Montelukast sodium released from chewable tablets was determined spectrophotometrically at 350 nm using distilled water with 0.5% SLS as blank.

### 4.5.5.11 STABILITY STUDIES [87]

Stability of a pharmaceutical product may be defined as the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, toxicological, protective and informational specifications.

**Why stability studies are necessary [88]**

- ✓ Stability study plays a central role in drug development
- ✓ Permit understanding of the molecule
- ✓ Essential for developing analytical method
- ✓ Essential for selecting packaging for drug substance and drug product
- ✓ Essential for choosing storage conditions for drug substance and drug product

### ACCELERATED STABILITY STUDIES [89]

Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid the undesirable delay, the principles of accelerated stability studies are adopted by accelerating the parameters such as temperature, humidity and light.

International Council of Harmonization (ICH) guidelines for "Stability testing of new drug substances for drug substance and product" (QIA) describes the stability test requirement for drug registration application in the European Union, Japan and United States of America. ICH guidelines specifies the length of study and storage conditions.

- ✓ Accelerated testing : 40 ± 2ºC & 75 ± 5% RH for 0,1,2,3 & 6 months.
- ✓ Long term testing : 25 ± 2ºC & 60 ± 5% RH for 0 & 12 months.

**Procedure**

Stability studies were carried out for optimized formulation (F-V) at 25±2°C/60C±5%RH and 40±2°C/75%±5%RH for 3 months. The selected clear ALU-ALU packed formulations were stored at 25±2°C/60C±5%RH and 40±2°C/75%±5%RH for 3 months and their physical appearance, average weight, thickness, hardness, friability, disintegration test, assay and *in vitro* drug release were evaluated at specified intervals of time (every month).

# CHAPTER- 5

# RESULTS AND DISCUSSION

The present study was undertaken to formulate sugar free Montelukast sodium chewable tablets by direct compression method using various disintegrants and superdisintegrants. The substance used as disintegrants and superdisintegrants are maize starch, pregelatinized starch, sodium starch glycolate, croscarmellose sodium and crospovidone. A total of five formulations (F-I to F-V) were prepared using various disintegrants and superdisintegrants.

The prepared blend of different formulations were evaluated for precompression parameters such as I.R spectral studies, angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. The prepared tablets were evaluated for various post compression parameters like appearance, thickness, hardness, weight variation, friability, disintegration test, wetting time, water absorption ratio, drug content, taste evaluation and *in vitro* dissolution studies. The optimized formulation was subjected for stability studies. The results were presented as follows in appropriate tables and figures.

# 5.1 PREFORMULATION STUDIES

## 5.1.1 ORGANOLEPTIC PROPERTIES

The organoleptic properties of Montelukast sodium was presented in Table. 10

**Table.10 Organoleptic Properties of Montelukast sodium (API)**

| Tests | Specification as per I.P | Observation |
|---|---|---|
| Color | Off white to pale yellow color | Off white to pale yellow color |
| Odor | Odorless | Odorless |
| Taste | Tasteless | Tasteless |

**Discussion:**

The organoleptic properties like color, odor and taste of the API were evaluated. The color of Montelukast sodium was found to be off white to pale yellow, no characteristic odor and no characteristic taste was observed in the study. Montelukast sodium showed similar color, odor and taste as per I.P specification.

## 5.1.2 SOLUBILITY TEST

The solubility profile of Montelukast sodium was presented in Table. 11

**Table.11 Solubility Analysis of Montelukast sodium (API)**

| Raw Material ( API ) | Solubility |
|---|---|
| **Montelukast sodium** | Soluble in water |
| | Freely soluble in ethanol, methanol |
| | Practically insoluble in acetonitrile |

**Discussion:**

The solubility analysis of drug indicates that Montelukast sodium is soluble in water, freely soluble in ethanol and methanol and practically insoluble in organic solvents.

### 5.1.3 DRUG - EXCIPIENTS COMPATIBILITY STUDIES

Compatibility studies were performed by preparing blend of different excipients with drug and stored at room temperature for one month. The blends were evaluated for every 15 days for changes like caking, liquefaction, discoloration and odor formation. The drug excipients compatibility profiles were shown in Table. 12

**Table. 12 Drug - Excipients Compatibility Studies**

| S. No. | Composition | Initial Period | After 15 days | After 30 days |
|---|---|---|---|---|
| 1 | Montelukast sodium | Off white to pale yellow color powder with no characteristic odor | *NCC | NCC |
| 2 | Montelukast sodium + Mannitol anhydrous | | NCC | NCC |
| 3 | Montelukast sodium + Maize starch | | NCC | NCC |
| 4 | Montelukast sodium + Pregelatinized starch | | NCC | NCC |
| 5 | Montelukast sodium + Sodium starch glycolate | | NCC | NCC |
| 6 | Montelukast sodium + Croscarmellose sodium | | NCC | NCC |
| 7 | Montelukast sodium + Crospovidone | | NCC | NCC |
| 8 | Montelukast sodium + Neo sucralose | | NCC | NCC |
| 9 | Montelukast sodium + Magnesium stearate | | NCC | NCC |
| 10 | Montelukast sodium + Methylparaben | | NCC | NCC |
| 11 | Montelukast sodium + Propylparaben | | NCC | NCC |
| 12 | Montelukast sodium + Iron oxide red | Brick red color powder | NCC | NCC |
| 13 | Montelukast sodium + Strawberry flavor | White color with strawberry odor | NCC | NCC |

*** NCC: No Characteristic Change**

**Discussion:**

From the above drug excipients compatibility study, it was observed that there was no characteristic change found between the drug and excipients. Thus it was concluded that the excipients selected for the formulation were compatible with Montelukast and suitable for formulation development.

## 5.2 FT- IR SPECTRAL STUDIES

FT- IR studies of the pure Montelukast sodium, disintegrant, superdisintegrant and combination of drug and superdisintegrants containing highest proportion were carried out to found any interaction between drug and excipients used in the formulation. FT- IR study was performed using IR spectroscopy (SHIMADZU). The I.R. Spectra of drug, disintegrants and superdisintegrant were shown in fig: 3 to 13 and in table 13 to 23 respectively. The comparison of FT- IR spectral data of drug with superdisintegrants was given in table 24.

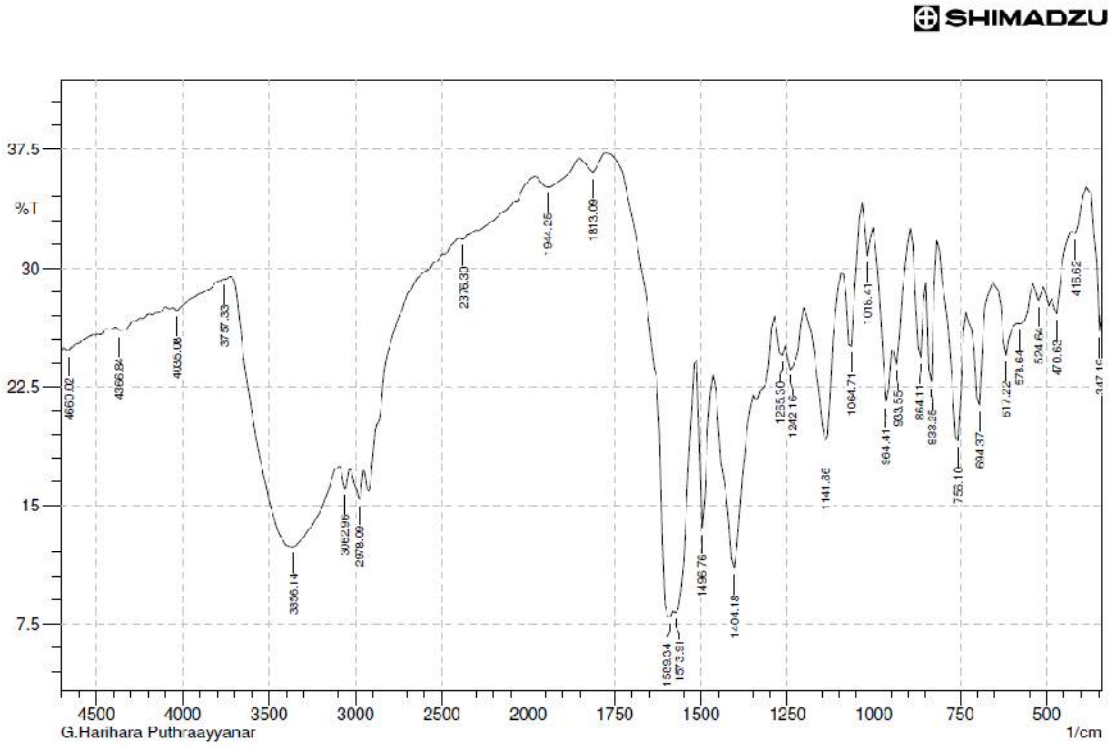



**Fig. 3 FT- IR Spectrum of Pure Montelukast sodium**

**Table. 13 FT- IR Spectral Data of Pure Montelukast sodium**

| S. No. | Wave Number ($cm^{-1}$) | Functional Group |
|---|---|---|
| **1** | 3356 | OH alcoholic group |
| **2** | 3062 | C-H aromatic stretching |
| **3** | 2978 | OH carboxylic |
| **4** | 1573 | C=C aromatic stretching |
| **5** | 1141 | C-N stretching |
| **6** | 756 | C-Cl |

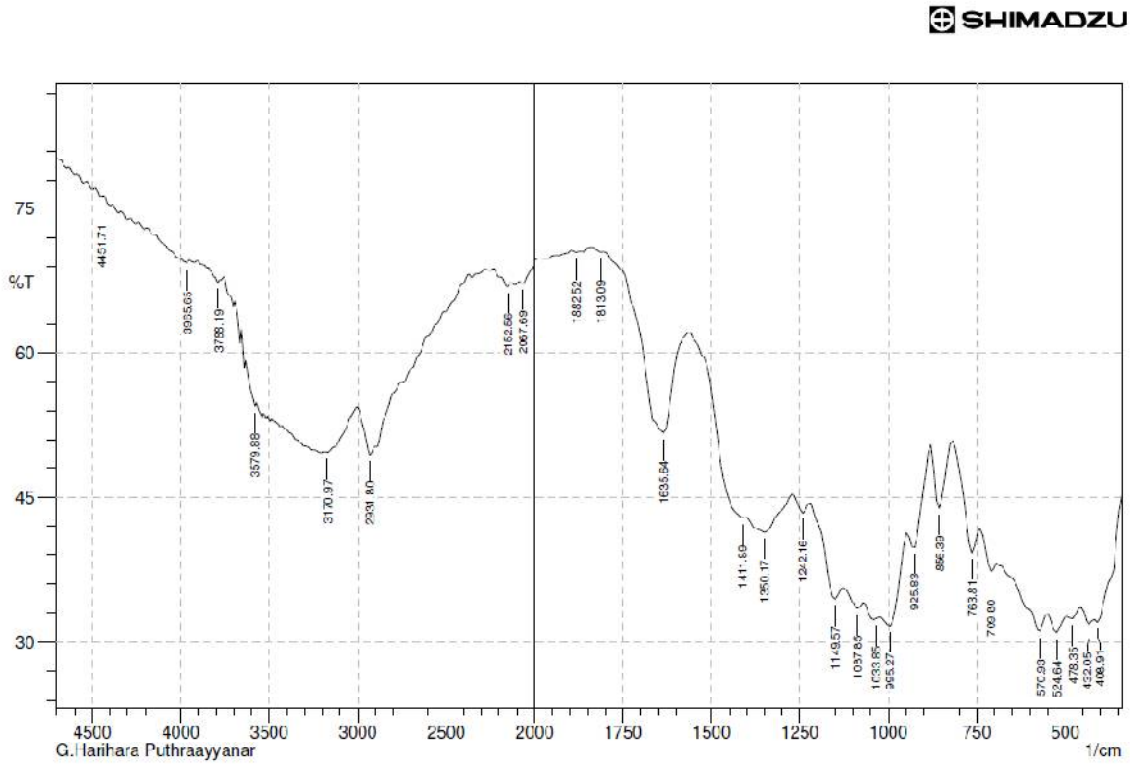



**Fig. 4 FT- IR Spectrum of Maize starch**

**Table. 14 FT- IR Spectral Data of Maize starch**

| S. No. | Wave Number ($cm^{-1}$) | Functional Group |
|---|---|---|
| **1** | 3170 | OH stretching |
| **2** | 2931 | C-H stretching |
| **3** | 1635 | Carbonyl C=O stretching |
| **4** | 1330 | C-H bending |

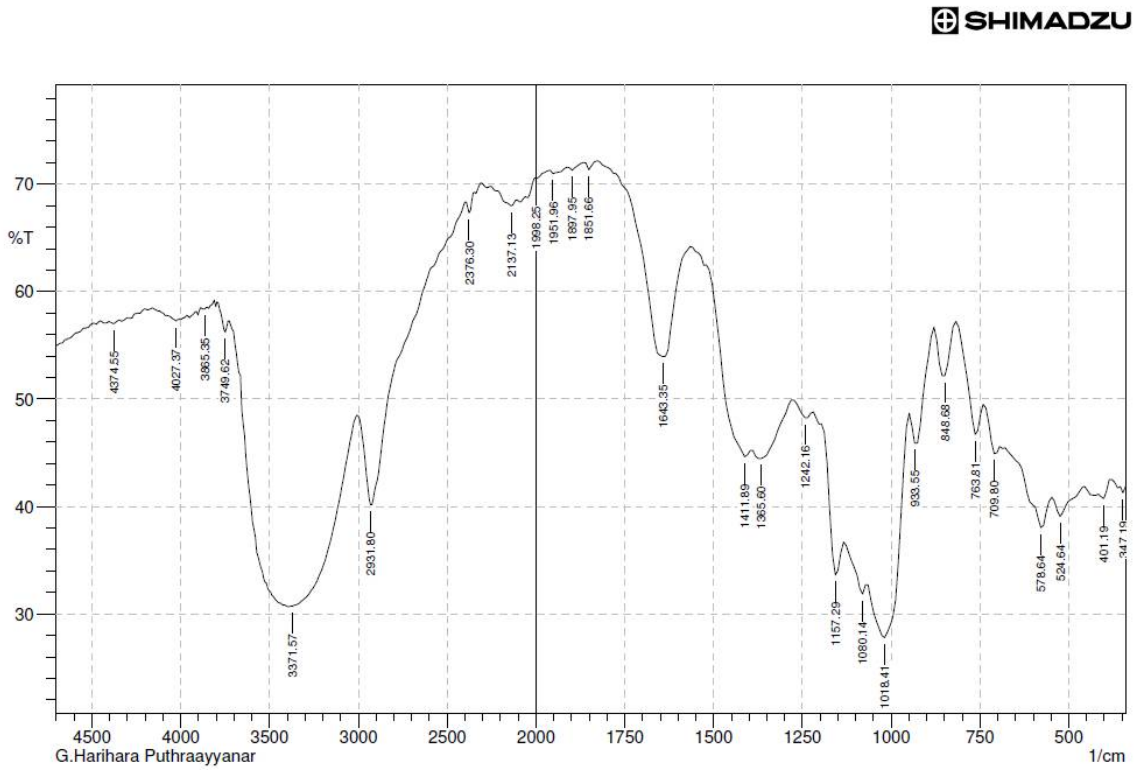



**Fig. 5 FT- IR Spectrum of Pregelatinized starch**

**Table. 15 FT- IR Spectral Data of Pregelatinized starch**

| S. No. | Wave Number ($cm^{-1}$) | Functional Group |
|---|---|---|
| 1 | 3371 | OH alcoholic stretching |
| 2 | 2931 | C-H stretching |
| 3 | 1643 | Carbonyl C= O stretching |
| 4 | 1365 | C-H bending |

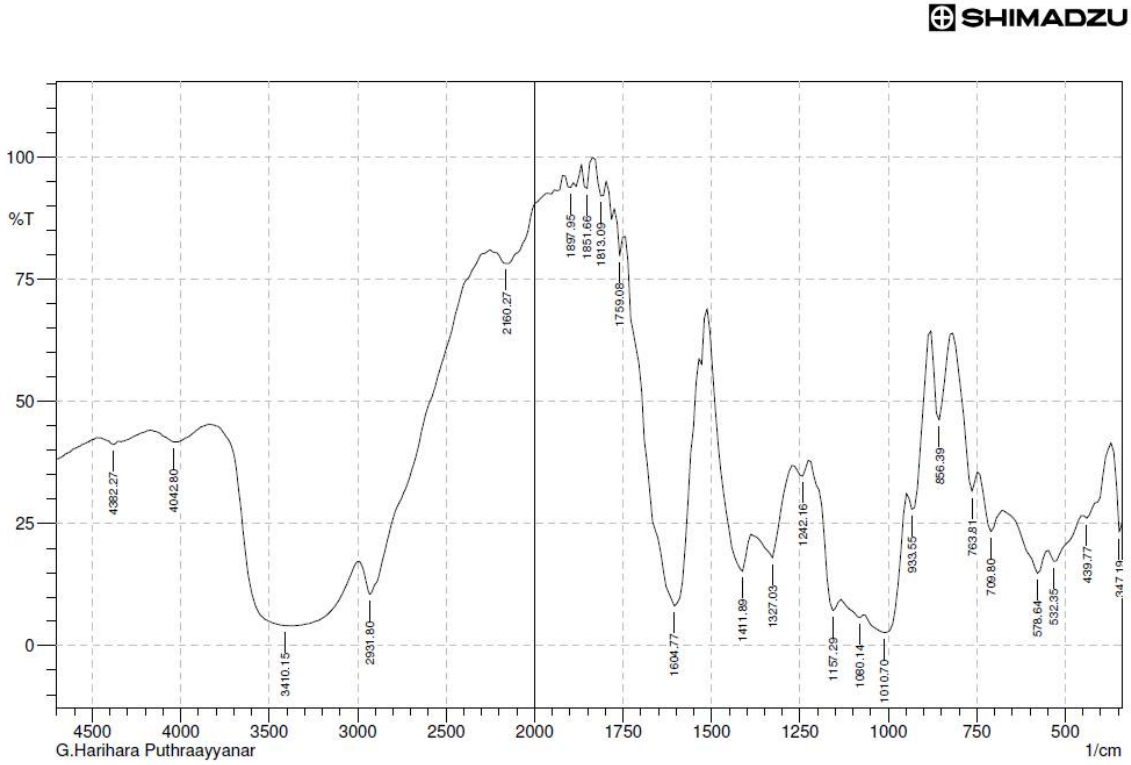



**Fig. 6 FT- IR Spectrum of Sodium starch glycolate**

**Table. 16 FT- IR Spectral Data of Sodium starch glycolate**

| S. No. | Wave Number ($cm^{-1}$) | Functional Group |
|---|---|---|
| 1 | 3282 | OH alcoholic stretching |
| 2 | 2931 | C-H stretching |
| 3 | 1604 | Carbonyl C=O stretching |
| 4 | 1327 | C-H bending |

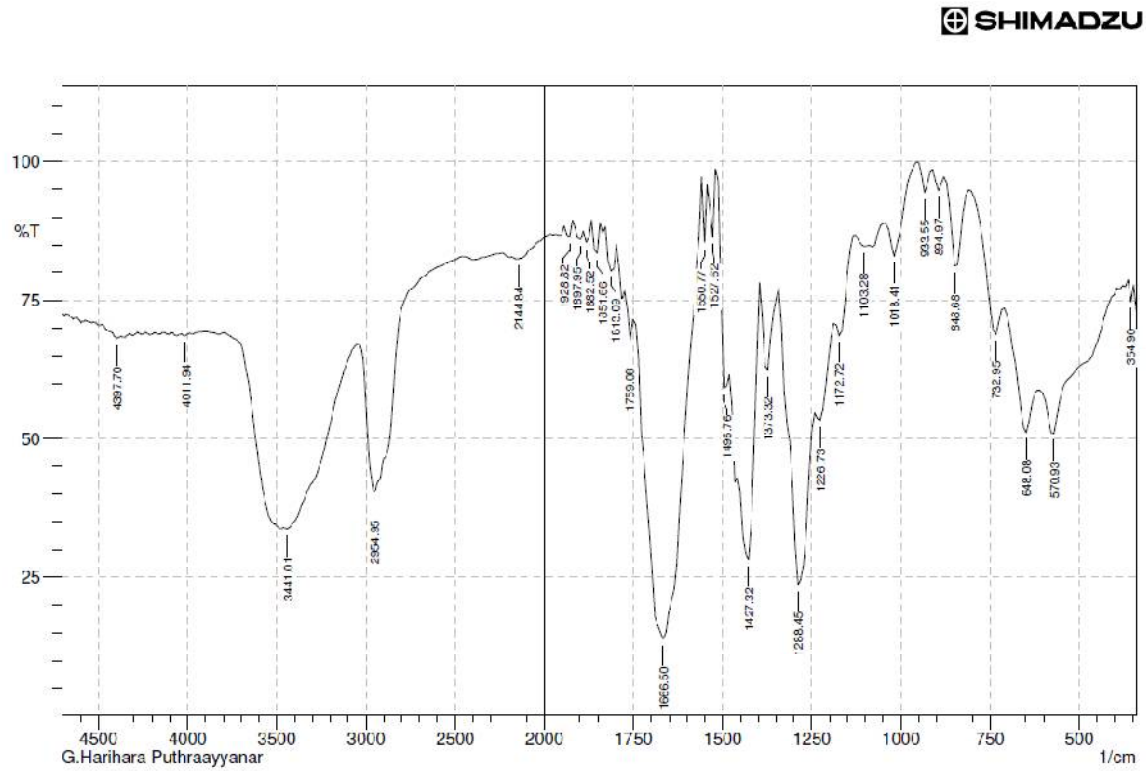



**Fig. 7 FT-IR Spectrum of Crospovidone**

**Table. 17 FT- IR Spectral Data of Crospovidone**

| S. No. | Wave Number ($cm^{-1}$) | Functional Group |
|---|---|---|
| 1 | 2954 | Alkane C-H stretching |
| 2 | 1666 | Alkane C-H bending |
| 3 | 1427 | Carbonyl C=O stretching |

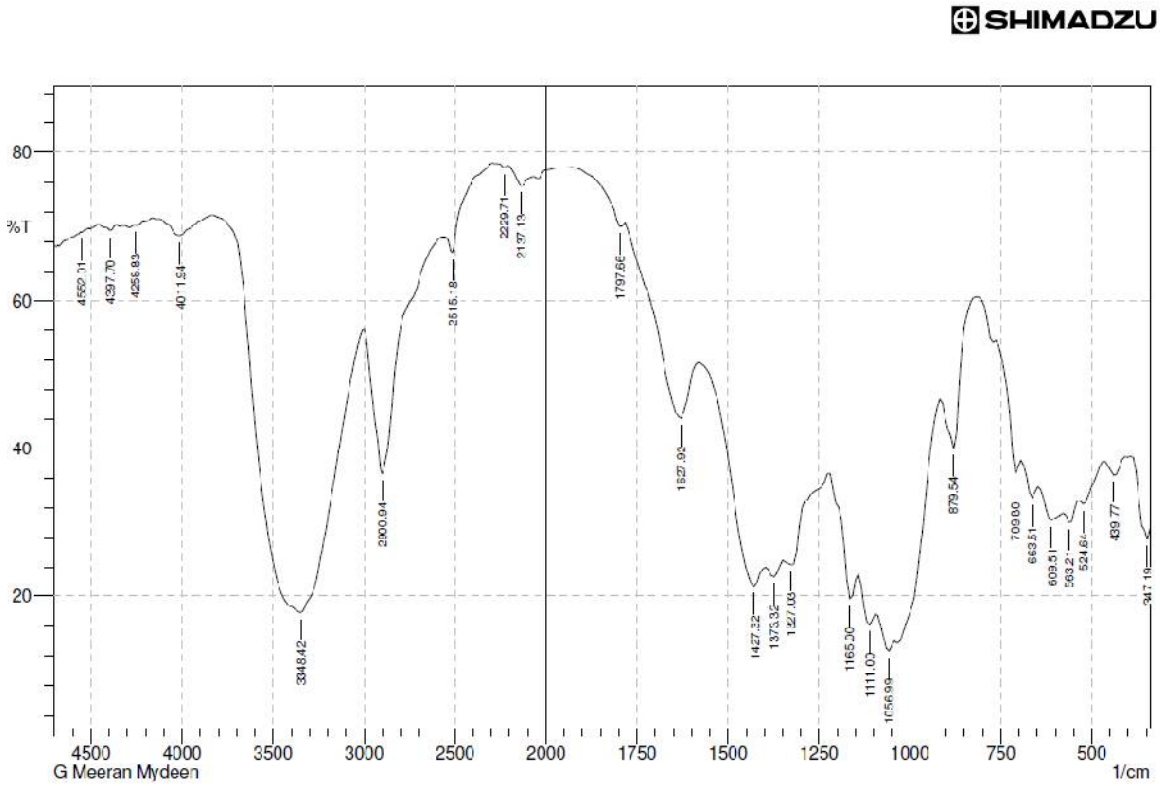



**Fig. 8 FT- IR Spectrum of Croscarmellose sodium**

**Table. 18 FT- IR Spectral Data of Croscarmellose sodium**

| S. No. | Wave Number ($cm^{-1}$) | Functional Group |
|---|---|---|
| 1 | 3348 | OH alcoholic stretching |
| 2 | 2900 | C-H stretching |
| 3 | 1627 | Carbonyl C=O stretching |
| 4 | 1327 | C-H bending |

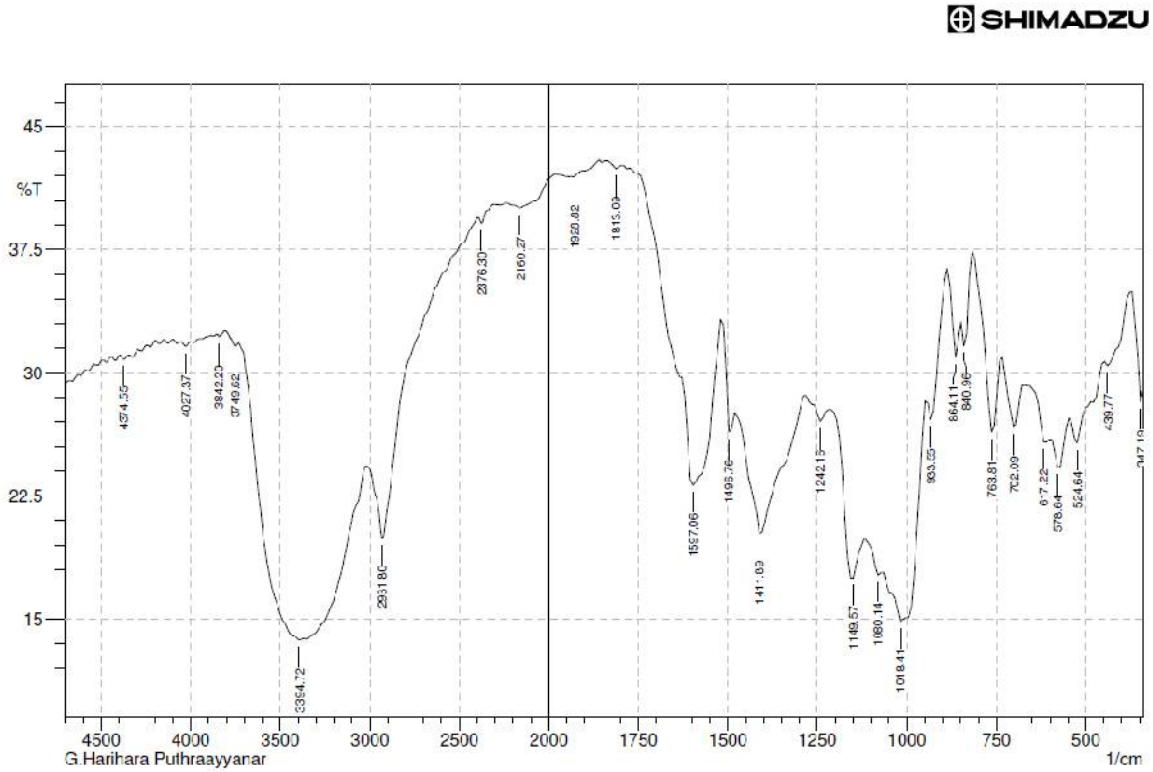



**Fig. 9 FT- IR Spectrum of Montelukast sodium + Maize starch**

**Table. 19 FT- IR Spectral Data of Montelukast sodium + Maize starch**

| S. No. | Wave Number ($cm^{-1}$) | Functional Group |
|---|---|---|
| 1 | 3394 | OH alcoholic group |
| 2 | 2931 | C-H stretching |
| 3 | 1597 | C=C aromatic stretching |
| 4 | 1411 | C-N stretching |
| 5 | 763 | C-Cl |

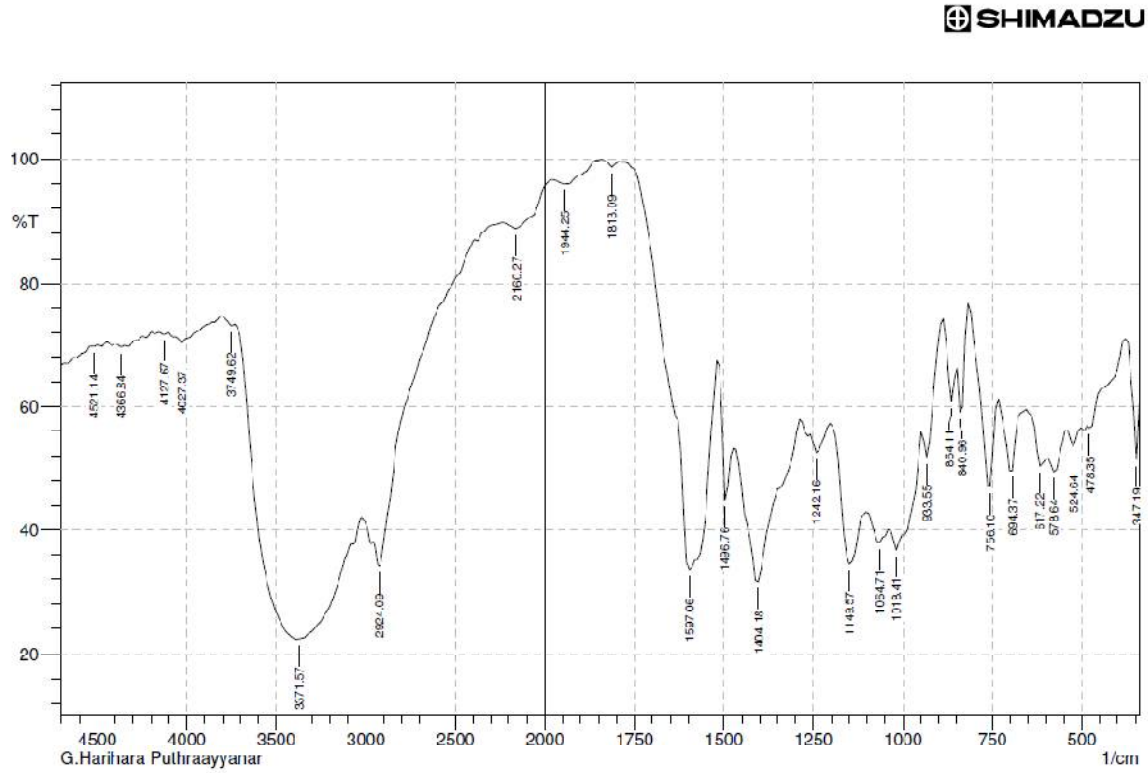



**Fig. 10 FT- IR Spectrum of Montelukast sodium + Pregelatinized starch**

**Table. 20 FT- IR Spectral Data of Montelukast sodium + Pregelatinized starch**

| S. No. | Wave Number ($cm^{-1}$) | Functional Group |
|---|---|---|
| 1 | 3371 | OH alcoholic stretching |
| 2 | 2924 | OH carboxylic |
| 3 | 1597 | C=C aromatic stretching |
| 4 | 1404 | C-H bending |
| 5 | 1149 | C-N stretching |
| 6 | 756 | C- Cl |

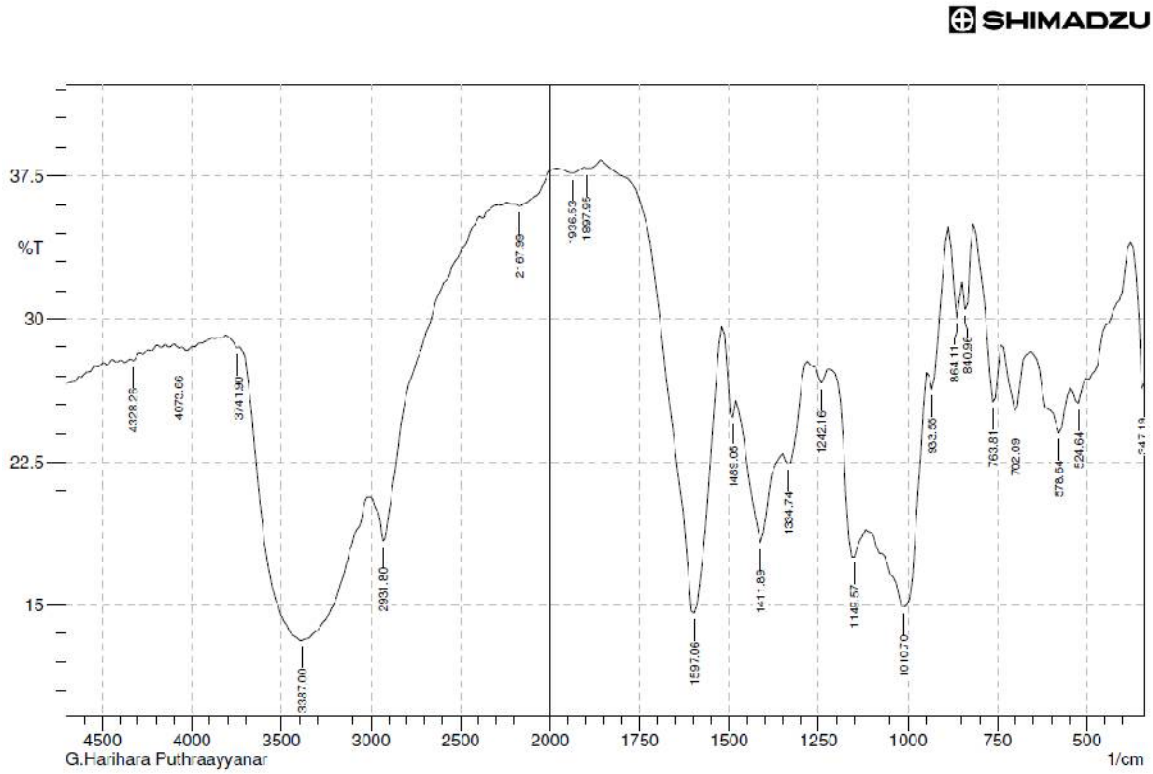



**Fig. 11 FT- IR Spectrum of Montelukast sodium + Sodium starch glycolate**

**Table. 21 FT- IR Spectral Data of Montelukast sodium + Sodium starch glycolate**

| S. No. | Wave Number ($cm^{-1}$) | Functional Group |
|---|---|---|
| 1 | 3387 | OH alcoholic stretching |
| 2 | 2931 | C-H stretching |
| 3 | 1597 | Carbonyl C=C stretching |
| 4 | 1334 | C-H bending |
| 5 | 1149 | C-N stretching |
| 6 | 763 | C-Cl |

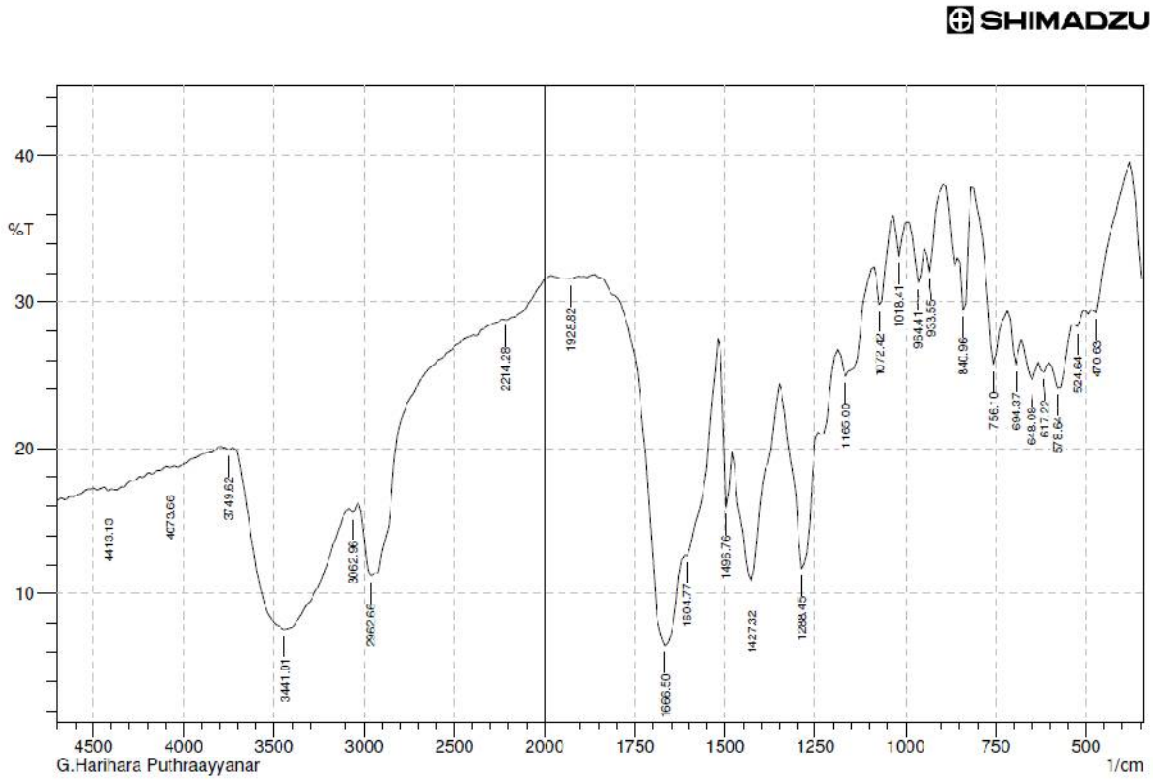



**Fig. 12 FT- IR Spectrum of Montelukast sodium + Crospovidone**

**Table. 22 FT- IR Spectral Data of Montelukast sodium + Crospovidone**

| S. No. | Wave Number ($cm^{-1}$) | Functional Group |
|---|---|---|
| 1 | 3441 | OH alcoholic stretching |
| 2 | 2931 | C-H stretching |
| 3 | 1597 | C=C alcoholic |
| 4 | 1334 | C=O carbonyl stretching |
| 5 | 1165 | C-N stretching |
| 6 | 756 | C-Cl |

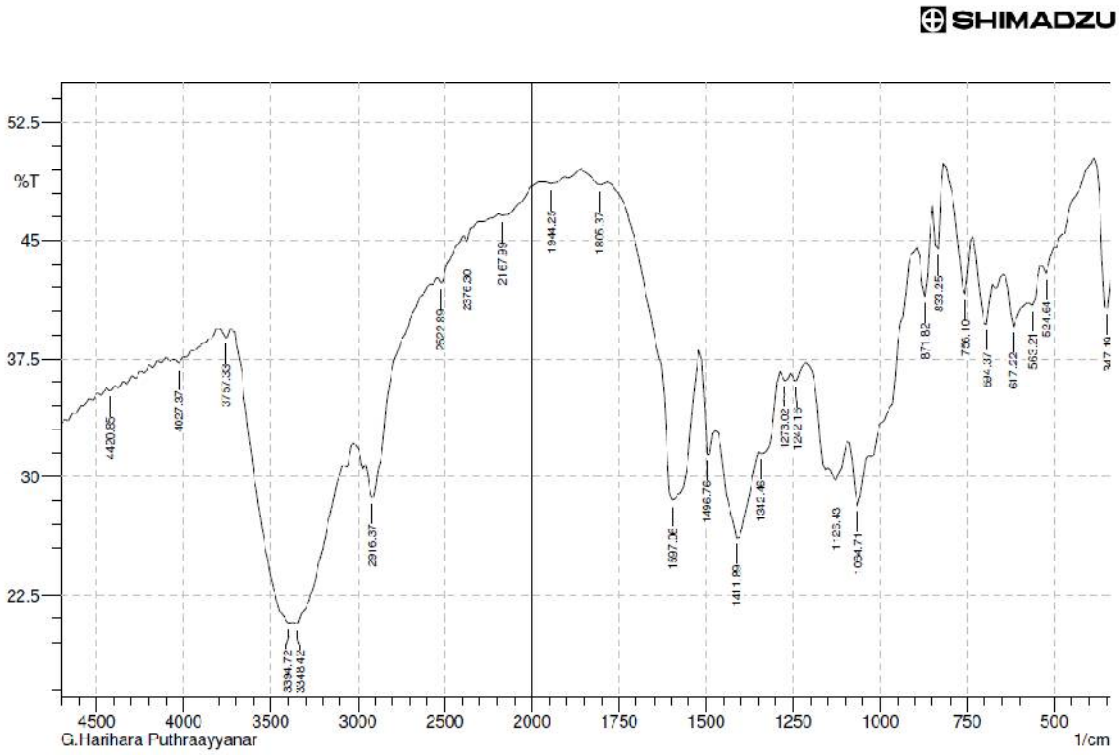



**Fig. 13 FT- IR Spectrum of Montelukast sodium + Croscarmellose sodium**

**Table. 23 FT- IR Spectral Data of Montelukast sodium + Croscarmellose sodium**

| S. No. | Wave Number ($cm^{-1}$) | Functional Group |
|---|---|---|
| 1 | 3394 | OH alcoholic stretching |
| 2 | 2916 | C- H stretching |
| 3 | 1627 | Carbonyl C=C stretching |
| 4 | 1342 | C-H bending |
| 5 | 1126 | C-N stretching |
| 6 | 756 | C-Cl |

**Table. 24 Comparative FT- IR Spectral Data of Drug, Disintegrants and Super disintegrants**

| Compounds | Functional Groups ($cm^{-1}$) | | | | |
|---|---|---|---|---|---|
| | **OH** | **C-H** | **C=C** | **C-N** | **C-Cl** |
| Drug (Montelukast sodium) | 3356 | 3062 | 1573 | 1141 | 756 |
| Drug+ Maize starch | 3394 | 2931 | 1597 | 1411 | 763 |
| Drug + Pregelatinized starch | 3371 | 2924 | 1597 | 1149 | 756 |
| Drug+Sodium starch glycolate | 3387 | 2931 | 1597 | 1149 | 763 |
| Drug+Croscarmellose sodium | 3394 | 2916 | 1627 | 1126 | 756 |
| Drug+Crospovidone | 3441 | 2931 | 1597 | 1165 | 756 |

**Discussion:**

FT- IR spectral studies indicated that the drug is compatible with all the excipients. The FT-IR spectrum of physical mixture showed all the characteristic peaks of Montelukast sodium, thus conforming that no interaction of drug occurred with the components of formulation.

## 5.3 EVALUATION OF PRECOMPRESSION PARAMETERS

### 5.3.1 MICROMERITIC PROPERTIES

The powder blends were evaluated for the following parameters such as angle of repose, bulk density, tapped density, compressibility index and hausner' ratio. The results were given below in Table. 25

**Table. 25 Precompression Parameters**

| Formulation Code | Angleof Repose (Θ) | Bulk Density ($g/cm^3$) | Tapped Density ($g/cm^3$) | Compressibility Index (%) | Hausner's Ratio |
|---|---|---|---|---|---|
| F-I | 29.3±0.1 | 0.305±0.2 | 0.361±0.2 | 16.2±0.2 | 1.18±0.2 |
| F-II | 27.1±0.4 | 0.309±0.6 | 0.357±0.3 | 16.0±0.9 | 1.18±0.7 |
| F-III | 27.0±0.1 | 0.303±0.5 | 0.354±0.1 | 15.5±0.4 | 1.19±0.5 |
| F-IV | 26.5±0.9 | 0.292±0.7 | 0.367±0.8 | 16.3±0.7 | 1.17±0.2 |
| F-V | 25.6±0.8 | 0.304±0.4 | 0.342±0.5 | 15.4±0.2 | 1.17±0.3 |

**All the values are expressed as mean ± SD, n=3**

**Discussion:**

The angle of repose of all formulations were found between $25^0$.60' to $29^0$.30' that is well within the specification limit of $25^0$- $29^0$ which indicates the flow type of powder blend was excellent. Formulation F-V showed better flow property.

The bulk density was found between 0.292 to 0.309 $g/cm^3$, tapped density was found between 0.342 to 0.367 $g/cm^3$. Compressibility index was found in the range of 15.4 to 16.3% which indicates the flow type of powder blend was fair. Hausner's ratio ranges between 1.17to 1.19. The above results in terms of micromeritic properties revealed that the flow property of all formulation was excellent and within the acceptable limit.

## 5.4 EVALUATION OF MONTELUKAST SODIUM CHEWABLE TABLETS

### 5.4.1 POST COMPRESSION PARAMETERS

#### 5.4.1.1 GENERAL APPEARANCE

The general appearance of all formulations (F-I to F-V) were examined and found as follows,

**Color** - Brick red color

**Shape** - Round

**Surface** - Smooth

**Cracks, depressions, pinholes –** Absent

The prepared tablets were evaluated for various post compression parameters. The results are presented in Table. 26

**Table. 26 Post Compression Parameters**

| Formulation code | Thickness (mm) | Hardness (kg /cm2) | Weight Variation (mg) | Friability (%) |
|---|---|---|---|---|
| F-I | 3.22±0.018 | 6.05±0.21 | 153.60±1.82 | 0.011±0.006 |
| F-II | 3.20±0.032 | 6.42±0.14 | 149.20±1.59 | 0.012±0.008 |
| F-III | 3.21±0.027 | 6.20±0.56 | 155.10±1.42 | 0.012±0.004 |
| F-IV | 3.20±0.041 | 6.65±0.17 | 151.90±1.78 | 0.014±0.009 |
| F-V | 3.22±0.032 | 6.15±0.56 | 150.80±1.29 | 0.013±0.012 |
| Marketed Sample | 2.81±0.16 | 7.00±0.1 | 153.01±2.32 | 0.012±0.05 |

**All the values are expressed as mean± SD, n=3**

**Discussion:**

**Thickness and Hardness**

The thickness of tablets was measured and were found in the range between 3.20±0.032 mm to 3.22±0.032 mm. All the formulation possessed uniform thickness. The hardness of the tablets was measured and the values were found in the range between 6.05±0.21 kg/cm$^2$ to 6.65±0.17 kg/cm$^2$. The prepared tablets possessed good mechanical strength with sufficient hardness. The thickness and hardness of marketed sample was found to be 2.81±0.16 mm and 7.00±0.1 kg/cm$^2$ respectively.

**Weight Variation and Friability Test**

All formulations of Montelukast sodium chewable tablets passed the weight variation test since the values are within the acceptable variation limit (±7.5%) of the tablet. Similarly percentage friability values of the prepared Montelukast sodium chewable tablets showed less than 1% weight loss that is highly within the acceptable limit. Hence all the tablets passed the friability test. Montelukast sodium chewable tablets were evaluated for various parameters and the results are given in Table.27.

**Table. 27 Evaluation of Montelukast sodium Chewable Tablets**

| Formulation Code | Disintegration Test (min) | Wetting Time (Sec) | Water Absorption Ratio (%) | Taste |
|---|---|---|---|---|
| F-I | 5.21±0.015 | 73±0.57 | 70.18±0.57 | Sweet |
| F-II | 5.07±0.064 | 70±0.57 | 86.88±0.56 | Sweet |
| F-III | 4.39±0.005 | 65±0.41 | 90.80±0.59 | Sweet |
| F-IV | 3.23±0.057 | 49±.53 | 93.2±0.57 | Sweet |
| F-V | 1.10±0.01 | 30±0.54 | 96.80±0.58 | Sweet |
| Marketed Sample | 2.42±0.025 | 39±0.43 | 92.14±0.57 | Sweet |

**All the values are expressed as mean± SD, n=3**

**Discussion:**

**Disintegration Time**

Disintegration time of Montelukast sodium chewable tablets were found between 1.10±0.01 to 5.21±0.015 minutes. Specification limit of disintegration time for uncoated tablet from I.P is NMT 15 minutes. Disintegration time of all formulations were found within the time as specified in the I.P and passed the disintegration test. The disintegration time of formulation-V containing crospovidone showed rapid disintegration (1.10±0.01 min) compared with other formulations.

**Wetting Time and Water Absorption Ratio**

Wetting time of all formulations were found between 30 to 73 seconds. Formulation V showed least wetting time (30 sec). Formulation V containing superdisintegrant such as crospovidone will quickly absorb water. Water absorption ratio of all formulations were found between 70% to 96%. The wetting time profiles of Montelukast sodium chewable tablets were shown in Fig. 14

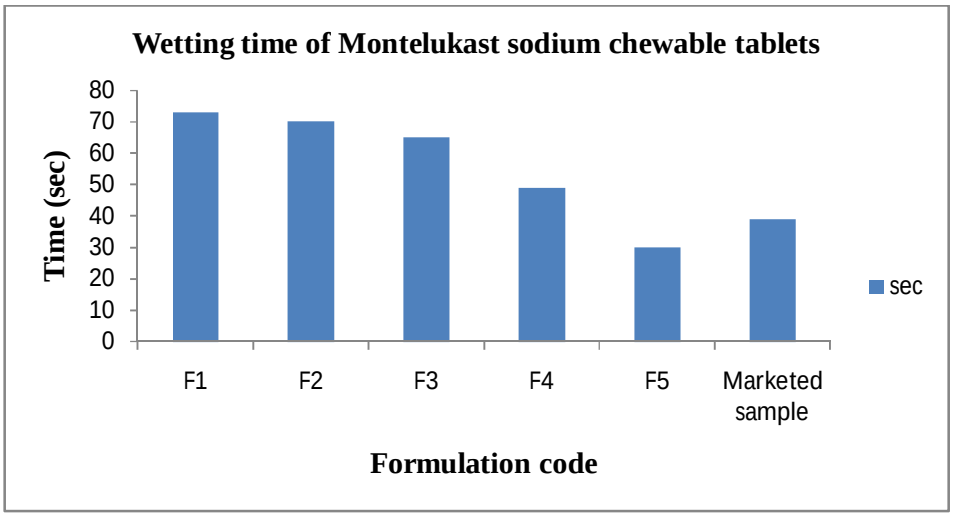


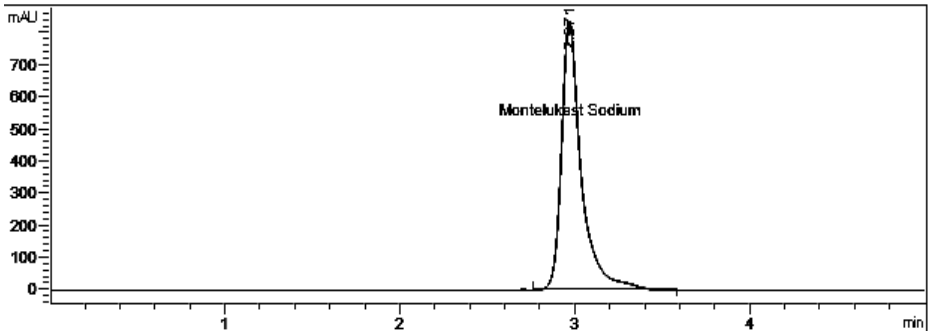

**Fig. 14 Wetting Time Profiles of Montelukast Chewable Tablets**

**Taste (Sensory Evaluation)**

Tasteless of the drug was changed in all formulations by using sugar free sweetening agent. All the formulations possessed sweet taste.

## 5.5 ASSAY

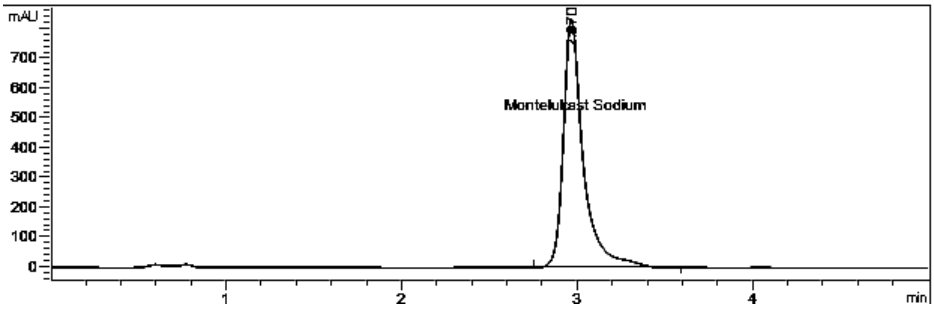
The assay was carried out according to the procedure given in methodology. The peak area plot of Montelukast sodium standard was given in Fig.15 and peak area plots of Montelukast sodium (Formulation F-I to F-V) were given in Fig.16 to 20 and the content of Montelukast sodium in chewable tablets were presented in Table. 28.




| S. No. | Name | RT* | Area | Plate count | Symmetry |
|---|---|---|---|---|---|
| 1 | Montelukast sodium | 2.971 | 6644957 | 4012 | 0.90 |

***RT- Retention Time**

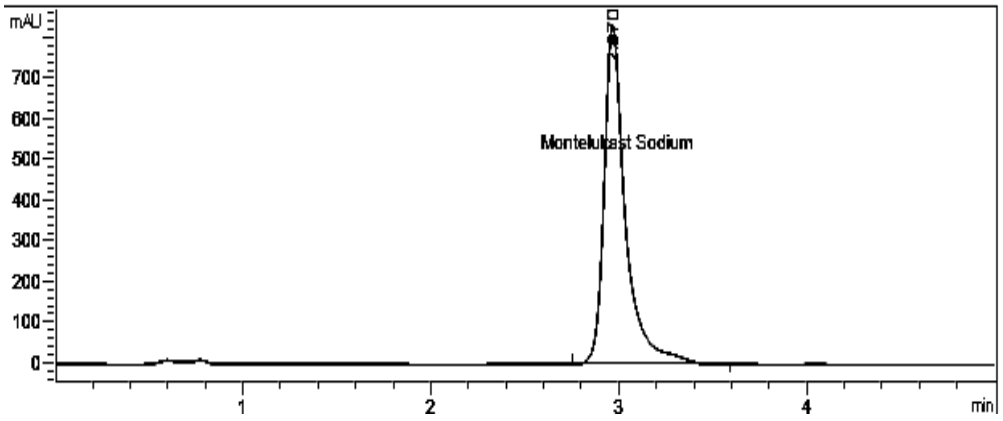
**Fig.15 HPLC CHROMATOGRAM OF MONTELUKAST SODIUM (Standard)**




| S. No. | Name | RT* | Area | Plate count | Symmetry |
|---|---|---|---|---|---|
| 1 | F-I | 2.970 | 6617882 | 4393 | 0.91 |

***RT- Retention Time**

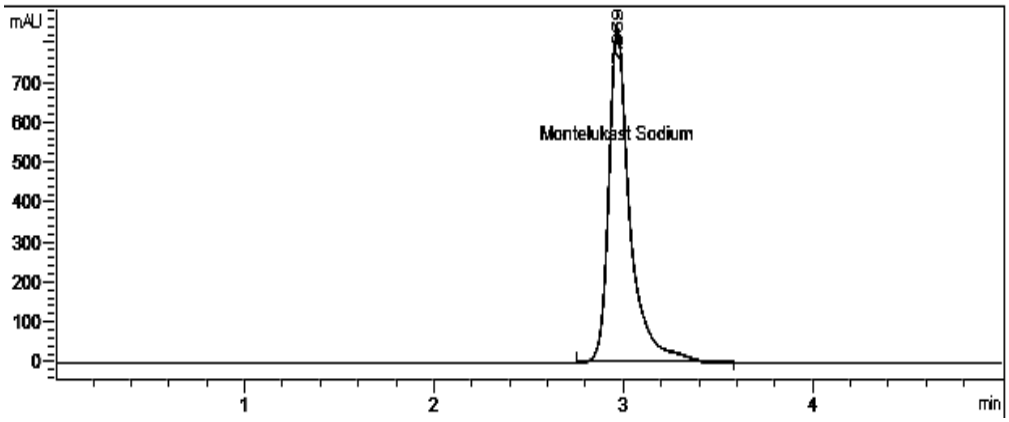
**Fig.16 HPLC CHROMATOGRAM OF FORMULATION F - I**




| S. No. | Name | RT* | Area | Plate count | Symmetry |
|---|---|---|---|---|---|
| 1 | F-II | 2.970 | 6639243 | 4105 | 0.91 |

***RT- Retention Time**

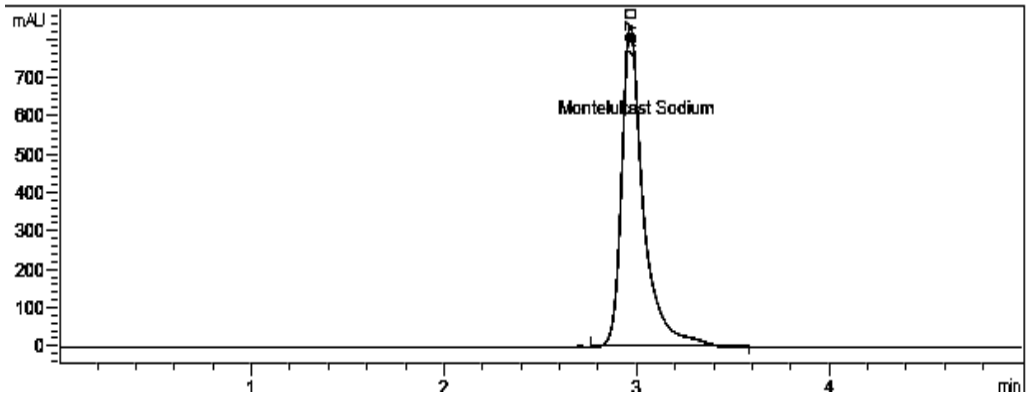
**Fig.17 HPLC CHROMATOGRAM OF FORMULATION F - II**




| S. No. | Name | RT* | Area | Plate count | Symmetry |
|---|---|---|---|---|---|
| 1 | F- III | 2.969 | 6644279 | 4197 | 0.90 |

***RT- Retention Time**

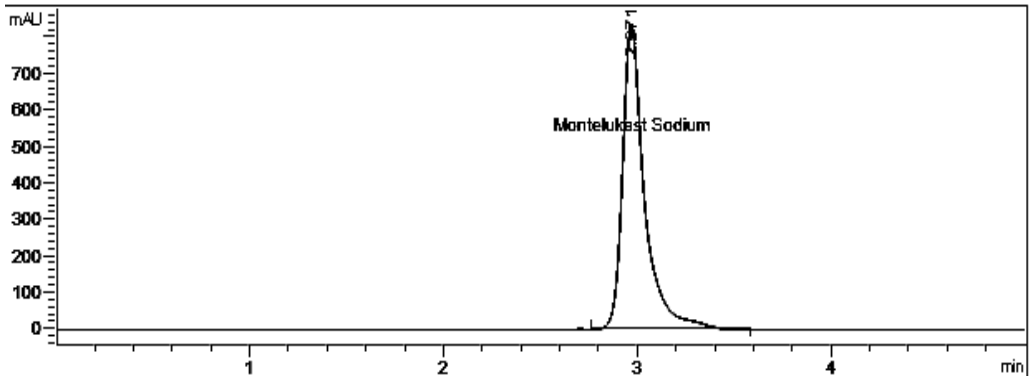
**Fig.18 HPLC CHROMATOGRAM OF FORMULATION F - III**




| S. No. | Name | RT* | Area | Plate count | Symmetry |
|---|---|---|---|---|---|
| 1 | F-IV | 2.970 | 6647313 | 4092 | 0.90 |

***RT- Retention Time**

**Fig.19 HPLC CHROMATOGRAM OF FORMULATION F - IV**




| S. No. | Name | RT* | Area | Plate count | Symmetry |
|---|---|---|---|---|---|
| 1 | F-V | 2.971 | 6644957 | 4012 | 0.90 |

***RT- Retention Time**

**Fig.20 HPLC CHROMATOGRAM OF FORMULATION F - V**

**Table.28 Assay of Montelukast sodium Chewable Tablets**

| Formulation Code | Limit(%) | Assay(%) |
|---|---|---|
| F-I | 90-110% | 100.70±1.50 |
| F-II | | 100.53±1.45 |
| F-III | | 100.89±2.86 |
| F-IV | | 101.52±1.24 |
| F-V | | 102.08±1.45 |
| Marketed sample | | 100.70±1.50 |

**Discussion:**

The content of Montelukast sodium is the chewable tablets were found in the range between 100.53 to 102.08%. The acceptable limit of Montelukast content as per I.P is 90 to 110%. The results revealed that the content of Montelukast sodium was within the acceptable limits in all the formulations.

## 5.6. CALIBRATION CURVE OF MONTELUKAST SODIUM

**Preparation of 0.5% of Sodium lauryl sulphate Solution[90]**

Place 0. 5 gm of sodium lauryl sulphate into a 100 ml volumetric flask and the volume was made up with de- mineralized water.

**Calibration Curve of Montelukast sodium**

0.025 gm of Montelukast sodium was accurately weighed and dissolved first in methanol and the volume was made upto 50 ml with de-mineralized water. From this 10ml was pipetted out and transferred into a 50 ml volumetric flask and make upto required volume using 0.5% SLS solution. This is secondary stock solution and from this various concentration of drug (5-50 µg/ml) were pipetted out separately into 10 ml standard flask and make upto required volume using 0.5% SLS solution and the absorbance of the resulting solutions were measured by using UV spectrophotometer at 350 nm. Standard curve of Montelukast sodium was given in the table.29 and fig.21

**Table.29 Calibration Curve Data of Montelukast sodium**

| S. No. | Concentration (µg/ml) | Absorbance (350 nm) |
|---|---|---|
| 1 | 5 | 0.0812 |
| 2 | 10 | 0.158 |
| 3 | 15 | 0.251 |
| 4 | 20 | 0.294 |
| 5 | 25 | 0.401 |
| 6 | 30 | 0.481 |
| 7 | 35 | 0.548 |
| 8 | 40 | 0.621 |
| 9 | 45 | 0.705 |
| 10 | 50 | 0.81 |

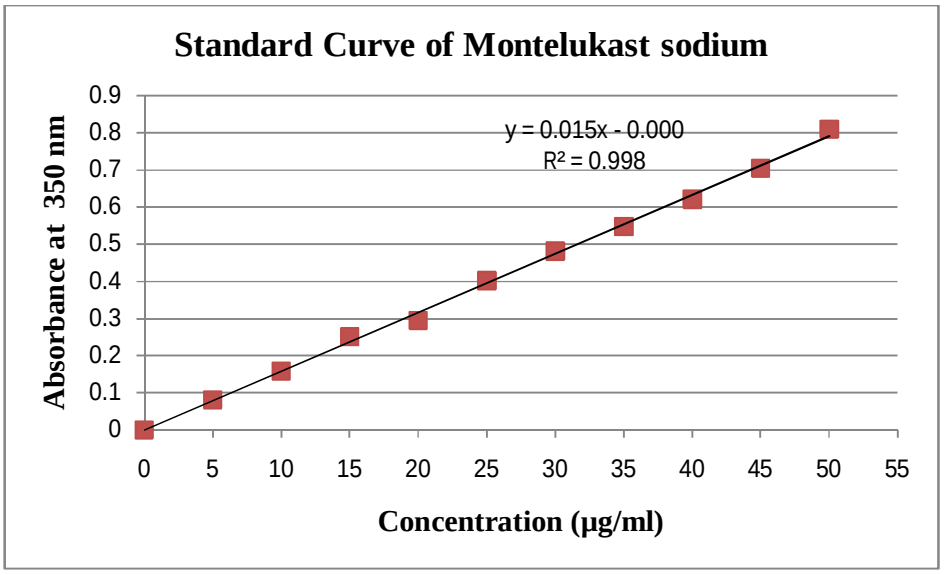



**Fig. 21 Standard Curve of Montelukast sodium**

## 5.7. *IN VITRO* DISSOLUTION STUDIES

The *in vitro* drug release studies of Montelukast sodium chewable tablets were given Table. 30 and fig: 22 respectively.

**Table. 30 *In Vitro* Drug Release Data of Montelukast sodium Chewable Tablets**

| Time (min.) | Percentage Drug Release (%) | | | | |
|---|---|---|---|---|---|
| | F – I | F – II | F - III | F – IV | F – V |
| **5** | 10.44±0.46 | 15.23±1.0 | 29.11±0.10 | 32.78±1.14 | 39.99±0.56 |
| **10** | 17.78±0.30 | 27.67±0.58 | 33.97±0.45 | 42.11±0.57 | 48.55±0.59 |
| **15** | 22.77±0.54 | 34.23±0.59 | 59.45±0.01 | 63.12±0.05 | 78.45±0.64 |
| **20** | 46.46±0.80 | 56.56±1.00 | 67.84±0.58 | 78.55±1.07 | 87.92±0.88 |
| **25** | 62.51±1.51 | 69.45±1.40 | 84.09±0.59 | 88.57±0.57 | 94.65±1.00 |
| **30** | 67.07±0.45 | 72.66±0.98 | 89.15±0.01 | 90.13±0.99 | 97.29±0.99 |

**All the values are expressed as mean± SD, n=3**

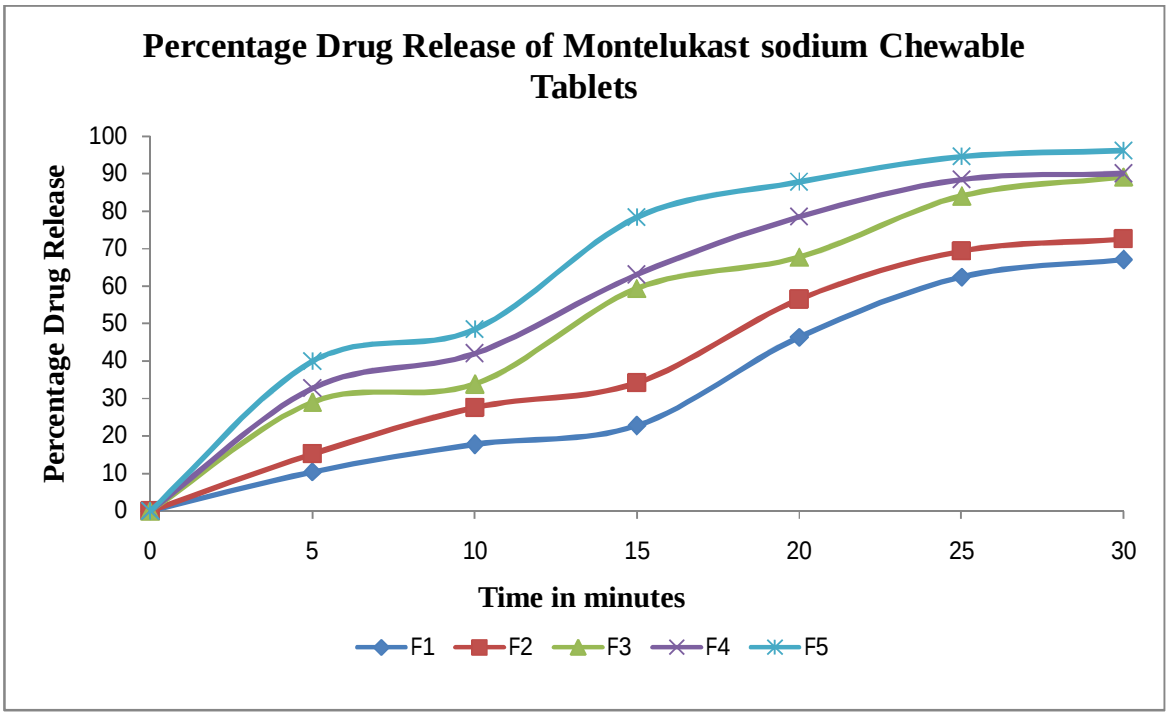



**Fig. 22 *In Vitro* Drug Release Profiles of Montelukast sodium Chewable Tablets**

**Discussion:**

Montelukast sodium chewable tablets was prepared by direct compression method using disintegrants like maize starch, pregelatinized starch and superdisintegrants like sodium starch glycolate, croscarmellose sodium and crospovidone. The dissolution study results are shown in table.30.

Montelukast sodium release was studied in 0.5% SLS solution for upto 30 minutes. The drug release of formulation F-I, F-II was found to be 67.07±0.45% and 72.66±0.98% at 30 minutes. The drug release of formulation F-III, F-IV and F-V was found to be 89.15±0.01%, 90.13±0.99% and 97.29±0.99% respectively. The acceptable *in vitro* dissolution limit for Montelukast sodium as per IP is NLT 80% of drug release at 30 minutes. Formulations F-III, F-IV and F-V passed the *in vitro* drug release studies.

Among the three formulations, formulation F-V containing crospovidone as superdisintegrant showed highest dissolution rates at the end of 30 minutes. They may be due to easy swelling ability and wicking capacity of crospovidone when compared to other disintegrants. The order of enhancement of the dissolution rate with various disintegrants and superdisintegrants was found to be crospovidone > croscarmellose sodium > sodium starch glycolate > pregelatinized starch > maize starch. Formulation F-V was taken as optimized formulation based on rapid disintegration time (1.10 minute), wetting time (30 sec) and *in vitro* dissolution profiles (97.29 %).

### 5.7.1 COMPARATIVE DISSOLUTION STUDY OF MARKETED FORMULATION AND OPTIMIZED FORMULATION (F-V)

The dissolution profile of optimized formulation (F-V) was compared with marketed Montelukast sodium chewable tablet. The comparative drug release profiles are shown in Table. 31 and fig.23.

**Table. 31 Comparative *In Vitro* Release Data of Montelukast sodium Marketed Tablet and Optimized Formulation (F-V)**

| Time (min.) | Percentage Drug Release | |
|---|---|---|
| | Formulation F-V | Marketed tablet |
| **5** | 39.99±0.56 | 30.09±0.11 |
| **10** | 48.55±0.59 | 43.30±0.55 |
| **15** | 78.45±0.64 | 59.47±0.90 |
| **20** | 87.92±0.88 | 68.33±1.01 |
| **25** | 94.65±1.00 | 77.57±0.62 |
| **30** | 97.29±0.99 | 88.01±0.83 |

**All the values are expressed as mean± SD, n=3**

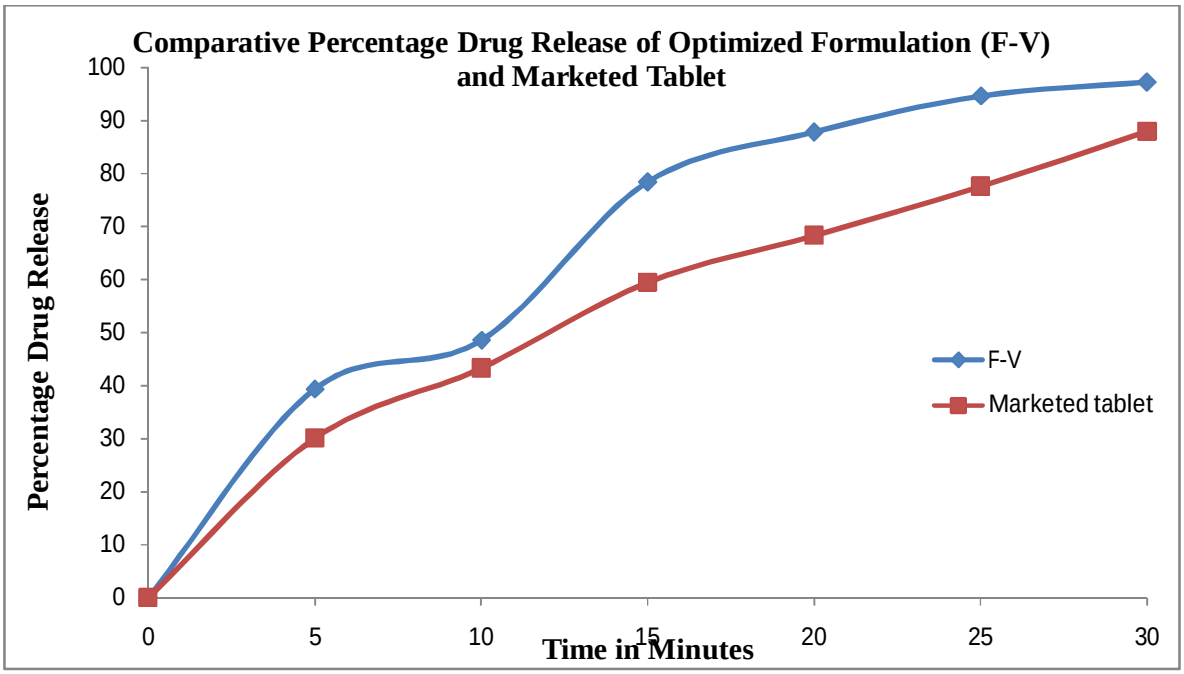



**Fig.23 Comparative *In Vitro* Drug Release Profiles of Montelukast sodium Marketed Tablet and Optimized Formulation (F-V)**

**Discussion:**

The percentage drug release of Marketed sample and optimized formulation (F-V) was found to be 88.01±0.83 % and 97.29 ±0.99 % at 30 minutes. The drug release of optimized formulation of Montelukast sodium chewable tablets was found to be greater than that of marketed product.

## 5.8 STABILITY STUDIES

The optimized formulation (F-V) was selected for the stability study and stored at 25±2°C/60%±5%RH and 40±2°C/75%±5%RH for a period of three months. The tablets were evaluated for various parameters like physical appearance, weight variation, thickness, hardness, friability, disintegration time, drug content and *in vitro* drug release at every month interval. The results are presented in Table 32 and 33.

**Table. 32 Stability Data of Optimized Formulation (F-V) Stored at 25±2°C/60%±5%RH**

| S. No. | Storage Conditions: 25±2°C/60%±5%RH | | | | |
|---|---|---|---|---|---|
| | **Parameters** | **Initial Period** | **1st Month** | **2nd Month** | **3rd Month** |
| 1 | Physical appearance | Brick red, round shaped tablets | Complies | Complies | Complies |
| 2 | Weight variation test (mg) | 150.8 | 150.74 | 150.63 | 150.21 |
| 3 | Thickness (mm) | 3.22 | 3.22 | 3.2 | 3.2 |
| 4 | Hardness ($Kg/cm^2$) | 6.15 | 6.15 | 6.15 | 6.1 |
| 5 | Friability (%) | 0.12 | 0.16 | 0.26 | 0.31 |
| 6 | Disintegration time (min.) | 1.10 | 1.21 | 1.45 | 1.47 |
| 7 | Drug content Limit (90-110%) | 102.08 | 102.06 | 102.06 | 102.04 |
| 8 | *In vitro* drug release at the end of 30 min. (%) | 97.29 | 97.25 | 97.21 | 97.2 |

**Table. 33 Stability Data of Optimized Formulation (F-V) Stored at 40±2°C/75%±5%RH**

| S. No. | Storage Conditions: 40±2°C/75%±5%RH | | | | |
|---|---|---|---|---|---|
| | **Parameters** | **Initial Period** | **1st Month** | **2nd Month** | **3rd Month** |
| 1 | Physical appearance | Brick red, round shaped tablets | Complies | Complies | Complies |
| 2 | Weight variation test (mg) | 150.8 | 150.99 | 150.87 | 150.21 |
| 3 | Thickness (mm) | 3.22 | 3.19 | 3.22 | 3.21 |
| 4 | Hardness ($Kg/cm^2$) | 6.15 | 6.15 | 6.17 | 6.17 |
| 5 | Friability (%) | 0.12 | 0.2 | 0.24 | 0.3 |
| 6 | Disintegration time (min.) | 1.10 | 1.21 | 1.45 | 1.00 |
| 7 | Drug content Limit (90-110%) | 102.08 | 102.05 | 102.05 | 102 |
| 8 | *In vitro* drug release at the end of 30 min. (%) | 97.29 | 97.22 | 97.18 | 97.11 |

**Discussion:**

Stability results revealed that there were no significant changes found in physical appearance, weight, thickness, hardness, friability, disintegration time, drug content and *in vitro* drug release during the period of 3 months even after stored at 25±2°C/60%±5%RH and 40±2°C/75%±5%RH. The results revealed that the drug was stable even after stored at 25±2°C/60%±5%RH and 40±2°C/75%±5%RH for three months.

# CHAPTER-6

# SUMMARY AND CONCLUSION

The present study was undertaken to formulate sugar free Montelukast sodium chewable tablets by direct compression method using various disintegrants and superdisintegrants. The substance used as disintegrants and superdisintegrants are maize starch, pregelatinized starch, sodium starch glycolate, croscarmellose sodium and crospovidone.

A total of five formulations (F-I to F-V) of sugar free Montelukast sodium chewable tablets were prepared by direct compression method. All the formulations were evaluated for both pre compression and post compression parameters as per the requirements of standards. Preformulation study of API such as organoleptic properties, solubility, compatibility study and FT- IR drug - excipients interaction study were carried out. The prepared blends were also evaluated for precompression parameters such as angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. The prepared tablets were evaluated for post compression parameters such as thickness, hardness, weight variation, friability, disintegration, wetting time, water absorption ratio, taste evaluation, assay and *in vitro* drug release study.

From the experimental results the following points can be summarized,

- ✓ In the preformulation study Montelukast sodium showed similar color, taste and odor as per the I.P specification. The results of drug excipients compatibility study showed that the excipients selected for the formulation were compatible with the API and suitable for formulation development.
- ✓ FT- IR spectral studies of pure drug and drug with excipients showed that there was no interaction between the drug and excipients used in the formulation.
- ✓ The results of micromeritic properties indicate that the flow property of formulation F-V showed better flow property compared with other formulations.
- ✓ All formulations possessed uniform thickness. The prepared tablets also possessed good mechanical strength with sufficient hardness.
- ✓ All formulations of Montelukast sodium chewable tablets passed the weight variation test since the values are within the acceptable variation limit (±7.5) of the tablet. All formulations of Montelukast sodium chewable tablets showed less than 1% weight loss and passed the friability test.

- ✓ Disintegration time of Montelukast sodium chewable tablets were found between 1.10±0.01 to 5.21±0.015 minutes. Formulation F- V showed least disintegration time (1.10±0.01 min) compared with all other formulations.
- ✓ Wetting time and water absorption ratio of Montelukast sodium chewable tablets were found to be in the range between 30 to 73 seconds and 70% to 96% respectively. Formulation F-V prepared using crospovidone as superdisintegrant showed least wetting time (30±0.54 sec) and high water absorption ratio (96.80±0.58%) among all formulation. All formulations showed good taste and better mouth feel.
- ✓ The content of Montelukast sodium in chewable tablets were found within the acceptable limits. (90-110%).
- ✓ In the *in vitro* drug release study, formulation F-V prepared using crospovidone as superdisintegrant showed maximum drug release (97.29%) at the end of 30 minutes.
- ✓ The obtained data suggested that formulation (F-V) containing crospovidone as super disintegrant showed better disintegration time(1.10±0.01 min), wetting time (30±0.54sec) and *in vitro* drug release (97.29%) and hence formulation F-V was considered as the optimized formulation based on rapid disintegration time ,wetting time and *in vitro* drug release.
- ✓ Comparative dissolution study of optimized formulation (F-V) and marketed product was carried out and the drug release of optimized formulation (F-V) was rapid (97.29%) compared to the marketed product (88.01%) at the end of 30 minutes. From the results it was concluded that the formulation F-V showed rapid drug release compared to the marketed product.
- ✓ The stability results of optimized formulation (F-V) indicated that there were no significant changes found in physical appearance, thickness, hardness, average weight, friability, disintegration, assay and *in vitro* drug release even after stored at 25±2°C/60%±5%RH and 40±2°C/75%±5%RH for 3 months. The results showed that the optimized formulation F-V was stable even after stored at 25±2°C/60%±5%RH and 40±2°C/75%±5%RH for a period of three months.

# CONCLUSION

From this study, the overall results revealed that the formulation F-V containing crospovidone as superdisintegrant was found to be better one which satisfied all the criteria for chewable tablets. The work concludes that Montelukast sodium chewable tablets could be successfully formulated by direct compression method using crospovidone as superdisintegrant which may improve the patient compliance, convenience in administration, therapeutic efficiency, better mouth feel making the formulation suitable for geriatric, bed ridden, diabetic and non diabetic patients.

# CHAPTER-7

# FUTURE STUDY

- ✓ Biopharmaceutical evaluation like *in vivo* study (Anti-histamine activity) can be performed in animals according to the guidelines approved by the "Committee of Purpose of Control and Supervision of Experiments on Animals (CPCSEA)". Ministry of social Justice and Empowerment, Government of India.
- ✓ Montelukast sodium tablet formulations may be evaluated for various Pharmacokinetic Parameters.
- ✓ The finding of the present study has initiated the company to go for scale up trial.

# CHAPTER – 8

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